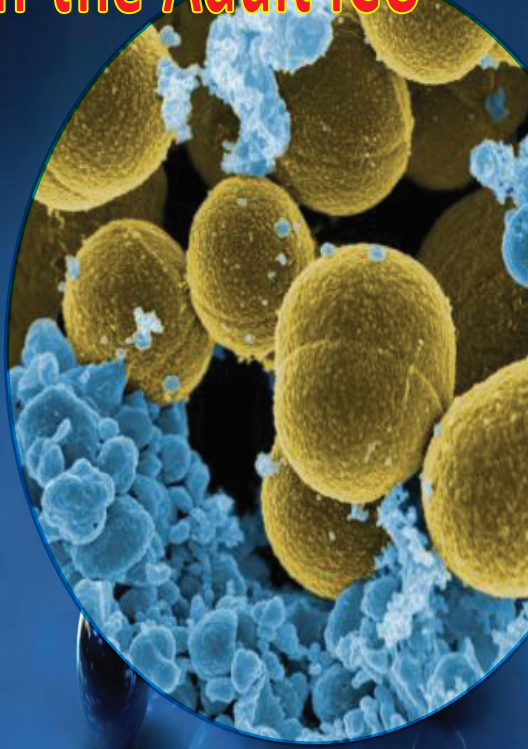
Guide to Antimicrobial Therapy in the Adult ICU 2012



Malaysian Society of Intensive Care

Dose schedules are being continually revised and new side effects recognised. The Writing Committee has endeavoured to ensure drug dosages are current and accurate. However the reader is strongly encouraged to always keep abreast with developments in drug information and clinical application.

Published by
Malaysian Society of Intensive Care (MSIC)
c/o MSIC Secretariat
Medical Academies of Malaysia
210 Jalan Tun Razak
50400 Kuala Lumpur

Pusat Kebangsaan ISBN Malaysia
ISBN 978 – 967 – 11415 – 2

Guide to Antimicrobial Therapy in the Adult ICU 2012

By Malaysian Society of Intensive Care

This guide can be downloaded from the Malaysian Society of Intensive Care website: www.msic.org.my

FOREWORD

Sepsis still remains one of the commonest cause of intensive care admission here in Malaysia. In the last six years following the first edition, there has been burgeoning increase in knowledge and usage of antimicrobials. However the pressing issues of growing antimicrobial resistance, inappropriate therapy and escalating cost compel for a more responsible prescriber.

In order to keep pace with important advances, most chapters have been revised and others eliminated. The objective of this book has not strayed from its original purpose that is to provide a quick and comprehensive guide for the Malaysian doctors caring for the critically ill. The structure has been kept to facilitate easy bedside referencing. The notations have expanded to explain the rationale behind antibiotic choices. Hence we hope this handbook will add to the armamentarium of those who work in intensive care units.

The first revision of the 'The MSA Guide to Antimicrobial Therapy in the Adult ICU' has been assumed by the Malaysian Society of Intensive Care. This guide has been a culmination of many hours of evidence review and exchange of opinions. Putting it together to cater to our local needs have been a challenge for us. We would like to thank our external reviewers for their invaluable input and also acknowledge the contribution of the working committee of the first edition: it is on the foundation of their work that the present, Second edition has been developed.

Dr Louisa Chan
Chairperson and Editor, Writing Committee for
Guide to Antimicrobial Therapy in the Adult ICU 2012

WRITING COMMITTEE

Dr Louisa Chan (Chairperson & Editor)
Consultant Intensivist
Dept. of Anaesthesia and Intensive Care
Hospital Kuala Lumpur

Associate Professor Dr Mohd Basri Mat Nor
Consultant Intensivist
Dept. of Anesthesiology and Intensive Care
Kulliyyah of Medicine
International Islamic University Malaysia

Dr Noor Airini Ibrahim
Senior Lecturer and Consultant Intensivist
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia

Dr Shanti Rudra Deva
Consultant Intensivist
Dept. of Anaesthesia and Intensive Care
Hospital Kuala Lumpur

Dr Tai Li Ling
Consultant Intensivist
Dept. of Anaesthesia and Intensive Care
Hospital Kuala Lumpur

EXTERNAL EXPERT REVIEWERS

(in alphabetical order)

Dato' Dr Hj Abdul Razak Muttalif
Director
Institute of Respiratory Medicine
Kuala Lumpur

Dr Claudia Cheng Ai Yu
Consultant Intensivist and
Anaesthesiologist
Loh Guan Lye Specialists Centre, Penang

Datuk Dr Christopher K.C Lee
Head of Department
Consultant Infectious Diseases Physician
Department of Medicine
Hospital Sungai Buloh

Dr Liew Ngoh Chin
Professor of Surgery
Department of Surgery
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia

Prof Dr Victor Lim
Vice President (Education)
International Medical University

Dr Nor'azim bin Mohd Yunos
Senior Lecturer and
Consultant Intensivist
Clinical School of Johor Bahru
Jeffrey Cheah School of Medicine and
Health Sciences
Monash University Sunway Campus

Prof Dr Rohaizak Muhammad
Breast and Endocrine Surgeon
Department of Surgery
University Kebangsaan Malaysia
Medical Centre

Dr Shanthi Ratnam
Consultant Physician and Intensivist
Hospital Sungai Buloh

Dr Tan Jit Ern Jonathan
Consultant Anaesthesiologist and
Intensivist
Director
Surgical Intensive Care Unit
Tan Tock Seng Hospital

TABLE OF CONTENTS

INTRODUCTION

Antimicrobials are commonly administered in the intensive care unit (ICU). This is in association with the high incidence of admissions with severe sepsis to ICUs and the increased risk of acquiring infections in ICU. In the Extended Prevalence of Infection in Intensive Care (EPIC II) study, an international study on the prevalence and outcomes of infections in ICUs, 51% of patients were infected while 71% were receiving antibiotics on the day of the study. Of the infected patients, 16% were being treated with antifungal agents. In Malaysia, 18.7% of patients had severe sepsis on admission to ICU in 2011.

In the EPIC II study, 75% of infected patients had positive microbial isolates; 62% of the positive isolates were Gram-negative, 47% Gram-positive, and 19% fungal. However, there was considerable variation in the types of organisms isolated among the different geographical regions. The proportion of Gram-negative organisms was more common in Asia, Western Europe and Latin America. Based on the Malaysian Registry of Intensive Care Report 2011, Gram-negative organisms accounted for 83.7% of the organisms causing ventilator-associated pneumonia (VAP); the most common organisms being *Acinetobacter spp*, *Klebsiella spp* and *Pseudomonas aeruginosa*. 61.9% of the causative organisms in VAP were of multi-drug resistant strains. In another study on catheter-related bloodstream infection in a Malaysian ICU, 38.9% of the isolates were *Klebsiella pneumoniae*, of which half of them were extended spectrum beta-lactamase (ESBL) producing strains.

Overall mortality from severe sepsis or septic shock ranges from 30% to 60%. The Surviving Sepsis Campaign (SCC) is a global effort to improve the care of patients with severe sepsis and septic shock. The SCC guidelines recommend starting intravenous

antibiotic therapy as early as possible once severe sepsis is diagnosed. In a recent retrospective cohort study in patients with septic shock, delay in the initiation of appropriate antimicrobial therapy after the onset of hypotension was associated with a significant increased risk of death. A study on compliance of SCC targets in the management of severe sepsis in ICUs in Asia, one of the three variables independently associated with hospital mortality was the delay in administration of antibiotics.

Antimicrobial use contributes to the emergence of resistant strains, which has become a major problem in ICUs worldwide. Antimicrobial stewardship and infection control are key components of a multifaceted approach to preventing emergence of antimicrobial resistance. Good antimicrobial stewardship involves selecting an appropriate drug, optimising its dose and duration to treat an infection while minimising toxicity and conditions for selection of resistant strains.

Bibliography:

1. *BMJ* 2011 Jun 13; 342: d3245. Epub 2011 Jun 13.
2. *Malaysian Registry of Intensive Care Report 2011*
3. *JAMA* 2009; 302(21): 2323-9
4. *Med J Malaysia* 2007; 62(5): 370-4
5. *Crit Care Med* 2006; 34(6): 1589-96

PRINCIPLES OF EMPIRICAL ANTIMICROBIAL THERAPY

Severe sepsis presents a diagnostic and management challenge to those who care for the critically ill patients. Besides adequate fluid resuscitation, vasopressor therapy and support of the failing organ systems, the use of appropriate antimicrobial therapy and adequate source control is equally important.

Empirical antimicrobial therapy should be guided by the knowledge of the most likely site of infection and likely organisms. All appropriate microbiological specimens including blood cultures should be obtained before commencing therapy whenever possible.

Inappropriate antimicrobial therapy is associated with poor outcomes. Moreover this can lead to the emergence of resistant organisms, antimicrobial-related adverse events and increase in healthcare costs.

The urgency to start antibiotics can be broadly classified as follows:

Category	Interval between diagnosis of suspected infection and administration of antibiotics	Examples
1. Emergency	Within 1 hour	• Severe sepsis or septic shock • Infections known to have a fulminant course e.g. meningococcaemia • Bacterial meningitis • Sepsis in splenectomised patients • Clinical evidence of infection in neutropenic patients

Category	Interval between diagnosis of suspected infection and administration of antibiotics	Examples
2. Urgent	> 1 hour	• Suspected infection in stable patients pending investigations e.g. suspected VAP, awaiting chest X-ray

When initiating appropriate empirical antimicrobials in patients with severe sepsis, consider the likely causative organisms, patient factors and properties of antimicrobials.

1. Likely causative organism

- *Decide if community or healthcare-acquired infection*
- *Identify the most likely source of infection*
  Take appropriate specimens for microscopy, culture and sensitivity testing. Imaging modalities may be necessary to locate the source of infection.
- *Consider local epidemiological data*
  Empiric antimicrobial choice depends on local susceptibility patterns. Knowing the resistance profiles in the community, hospital or unit helps in choosing antimicrobials appropriately.

2. Patient factors

- *Severity of illness*
  Patients in severe sepsis or septic shock require emergent and broad spectrum antimicrobial therapy.
- *Prior antimicrobial use or prolonged hospitalisation*
  Both are risk factors for the presence of resistant organisms.
- *Immunosuppressive states*
  Patients with underlying malignancy, malnutrition, on steroids or immunosuppressive drugs may require broad-spectrum therapy including antifungal.

- *Presence of renal or hepatic dysfunction*
  The risk-benefit of the antimicrobial must be determined on a case-to-case basis. Maintenance doses are adjusted in line with the severity of organ dysfunction.
- *Others*
  Pregnancy, drug allergy

3. Antimicrobial profile

- *Route of administration*
  The intravenous route should always be used in severe sepsis as oral absorption is unpredictable even in drugs with good oral bioavailability.
- *Dose and interval*
  Pathophysiological changes in critically ill patients alter the pharmacokinetic (PK) and pharmacodynamic (PD) profile of the antimicrobials. Antibiotics can be categorised into three different classes depending on the PK/PD indices associated with their optimal killing activity.

Classification	**PK/PD index**	**Goals of Therapy**	**Examples**
Time-dependent	T>MIC Percentage of time where drug concentration remains above MIC during a dosing interval	Maximise duration of exposure (Refer to **Appendix C** for extended infusion of ß-lactams)	Penicillins Cephalosporins Carbapenems Clindamycin
Concentration-dependent	C_{max}/MIC Ratio of peak concentration to MIC	Maximise concentration of drug	Aminoglycosides Polymyxin

Classification	PK/PD index	Goals of Therapy	Examples
Concentration-dependent with time dependence	AUC_{0-24}/MIC Ratio of area under concentration-time curve (AUC) during a 24-h period to MIC	Maximise amount of drug	Fluoroquinolones Vancomycin Azithromycin Linezolid Tetracyclines

MIC: Minimum Inhibitory Concentration

- *Achievable antimicrobial concentrations in tissue*
  Aminoglycosides and glycopeptides penetrate tissues poorly. Aminoglycosides should not be used as monotherapy while a higher plasma level of glycopeptides is recommended to ensure adequate tissue penetration. Both ß-lactams and quinolones have good tissue penetration.
- *Post antibiotic effect (PAE)*
  This is defined as persistent suppression of bacterial growth even after the serum antibiotic concentration falls below the MIC of the target organism. Aminoglycosides and fluoroquinolones have post antibiotic effect against gram negative bacteria.
- *Adverse events*
  Risk-benefit of antimicrobials with potential serious adverse events should be considered on a case-to-case basis. If unavoidable, serum levels should be monitored for toxicity (e.g. aminoglycosides).
- *Ecological profile*
  Limit the use of antimicrobials with known potential for selecting resistant organisms and associated risks of superinfection e.g. third generation cephalosporins (selection pressure for ESBL producing Enterobacteriaceae).

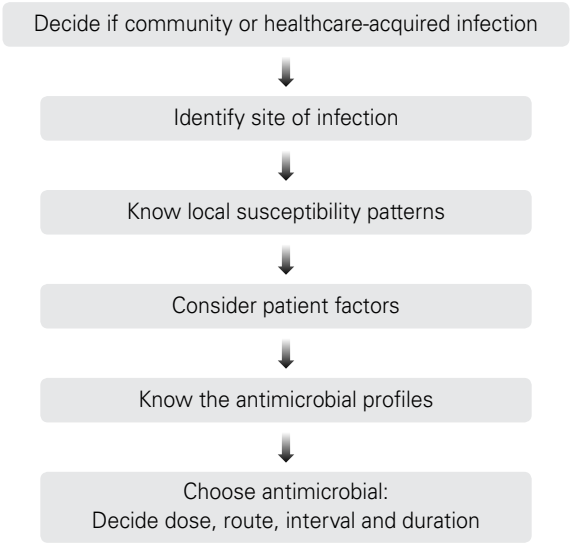
Empirical therapy should be re-evaluated after 48-72 hours or when culture results become available. Once a causative pathogen is identified, narrow the spectrum of antimicrobial therapy (de-escalation). Sensitivity tests should be interpreted carefully. In vitro sensitivity does not equate with clinical effectiveness (e.g. ESCAPPM organisms: *Enterobacter spp, Serratia spp, Citrobacter freundii, Aeromonas spp, Proteus vulgaris, Providencia spp, Morganella morganii*).

If the patient is improving, the recommended duration of antimicrobial therapy is 5 to 7 days. There is increased risk of resistance with prolonged use of antimicrobials. Certain conditions may require prolonged therapy e.g. *P. aeruginosa* sepsis, complicated *S. aureus* infections and infective endocarditis. Consider switching to the oral route whenever possible.

If there is no clinical response within 48-72 hours, consider:

- The possibility of a secondary infection
- The presence of resistant organisms
- Abscesses that are not drained or infected foreign bodies that are not removed
- Inadequate penetration of antimicrobial to the site of infection
- Inadequate spectrum of antimicrobial coverage
- Inadequate dose/interval
- Non-infectious causes e.g. deep vein thrombosis, acute myocardial or pulmonary infarctions, acute pancreatitis, hyperthyroidism, Addisonian crisis, malignancies and central nervous system hemorrhages.

Pathway in choosing the empirical antimicrobial



MICROBIOLOGICAL INVESTIGATIONS

Identification of causative organisms is central to effective antimicrobial therapy. Whenever possible, appropriate cultures should always be obtained before commencing antimicrobials.

Below are some common microbiological investigations that are relevant to the intensive care practice.

Blood specimen

All septic patients (irrespective of source) should have blood cultures taken prior to commencement of antimicrobials.

The volume of blood determines the yield of positive result in blood culture. A minimum of 20 ml of blood should be drawn; 10 ml for each aerobic and anaerobic bottle. Increasing the volume to 40-60 ml from different venepuncture sites (obtaining 2-3 pairs of blood cultures) has been shown to increase the yield further. In endocarditis, 3 pairs of blood cultures taken at least an hour apart is required to confirm constant bacteraemia but administration of antimicrobials should not be delayed in severely ill patients. If catheter-related blood stream infection is suspected simultaneous blood sampling from the peripheral blood and catheter hub needs to be taken.

When disseminated tuberculosis (TB) or fungaemia is suspected, BACTEC® Myco/F Lytic culture bottles should be used to improve yield of these suspected organisms.

Blood can be taken for serological testing to diagnose atypical pneumonias, leptospirosis, melioidosis, toxoplasmosis, rickettsial and typhoid infections.

Blood tests for viral infections include serology for herpes simplex type 1 and 2, cytomegalovirus (CMV), dengue, viral hepatitis and respiratory viruses. Consider Human Immunodeficiency Virus (HIV) serology in patients at risk. Viral cultures are not routinely performed.

The diagnosis of malaria requires 3 sets of thick and thin blood smear preparations taken over a 48 hour period (at 6, 12 and 48 hour). In smear negative patients, in which malaria is stll strongly suspected blood for malarial polymerase chain reaction (PCR) can be sent.

Respiratory specimen

A good specimen of sputum or tracheal aspirate for Gram stain and cultures should have less than 10 epithelial cells per low power field reflecting a lower respiratory tract sample. Special stains can be requested to diagnose *Pneumocystis jiroveci* or *Mycobacterium tuberculosis.*

Most laboratories report the results of sputum and tracheal aspirate cultures semi-quantitatively; either as light, moderate or heavy growth. A positive culture does not differentiate true pathogens from colonisers. Results must be interpreted in the context of the clinical condition to prevent unnecessary antimicrobial use. If quantitative test is available, the threshold for diagnosing ventilator-associated pneumonia (VAP) with tracheal aspirate is 10^5 or 10^6 cfu/ml.

Respiratory specimens can also be obtained invasively by performing bronchoalveolar lavage (BAL) or protected specimen brushing (PSB). Both specimens need to be analysed quantitatively based on the number of colony forming units (cfu). The threshold for diagnosing VAP with BAL is 10^4 or 10^5 cfu/ml and with PSB is 10^3 cfu/ml. Indications for BAL include non-resolving pneumonia,

diffuse lung infiltrates in the immunocompromised host or quantitative cultures for VAP.

Nasopharyngeal swabs and the above respiratory specimens can be sent using appropriate viral transport media for viral serology and PCR tests. Viral cultures are not routinely performed. The viruses commonly investigated are influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus and CMV. Viral detection does not preclude concurrent bacterial infection.

Pleural fluid specimen

Normal pleural fluid has the following characteristics:

- clear ultrafiltrate of plasma
- pH 7.60-7.64
- protein content less than 20 g/L
- less than 1000 leucocytes/mm^3
- glucose concentration similar to that of plasma
- lactate dehydrogenase (LDH) level less than 50% of plasma

In diseased conditions, pleural fluid can be classified into exudative or transudative. Infective causes of exudative pleural effusion are bacterial, tuberculous or viral pneumonias. According to Light's criteria, a pleural effusion is likely exudative if at least one of the following exists:

- Pleural fluid/serum protein > 0.5 or absolute pleural protein > 30 g/L
- Pleural fluid/serum LDH > 0.6
- Pleural fluid LDH level > 2/3 upper limit of normal serum value

An exudative pleural fluid needs to be correlated with the other analysis below to determine if it is of an infective cause.

1. Microscopic examination
   Pleural fluid for leucocytes and differential cell count should be sent in an anticoagulated tube. Leucocyte count

> 10,000 /mm^3 strongly suggests infection while counts > 50,000 /mm^3 is usually seen in empyema. Predominance of polymorphs is suggestive of bacterial infection while lymphocytic predominance is suggestive of TB, resolving pneumonia or fungal infections. Gram stain is done to enable direct observation of bacteria or fungi under microscopic examination.

2. Smear for acid-fast bacilli
   Pleural fluid smears are rarely positive for acid-fast bacilli (< 10% of proven PTB).

3. Glucose
   Pleural fluid glucose levels < 3.3 mmol/L is suggestive of infection. Levels of 1.7 – 2.8 mmol/L suggests tuberculous infection while levels < 1.7 mmol/L suggests bacterial empyema.

4. pH
   Pleural fluid pH < 7.2 is suggestive of infection. Pleural fluid pH < 7.1-7.2 is more predictive of complicated effusions and indicates the need for urgent drainage of the effusion, while pleural fluid pH > 7.3 suggests that the effusion may be managed with systemic antibiotics alone.

5. Lactate dehydrogenase
   Pleural fluid LDH levels > 1000 IU/L suggest complicated parapneumonic effusions.

6. Culture and susceptibility testing
   Culture of infected pleural fluid yields positive results in approximately 40% - 60% of cases. Diagnostic yields, particularly for anaerobic pathogens, may be increased by directly culturing pleural fluid into blood culture bottles.

For *Mycobacterium tuberculosis*, the use of broth medium (e.g. BACTEC) provides higher yields and faster results (1-2 weeks) than conventional methods.

7. Polymerase chain reaction (PCR) for tuberculous DNA
   PCR findings are positive in almost all of culture-positive TB pleural fluids but in only 30 - 60% of culture-negative pleural fluids.

8. Pleural adenosine deaminase (ADA)
   If lymphocyte predominant in exudate, ADA of > 40 U/L has a 90-100% sensitive and 85-95% specific for TB pleuritis.

Cerebrospinal fluid specimen

Lumbar puncture should only be performed after a neurological examination but should never delay the administration of antimicrobials. A CT scan to rule out raised intracranial pressure prior to lumbar puncture is indicated in patients with the following: age > 60 years, history of central nervous system (CNS) lesion, seizure within 1 week of presentation, focal neurological signs, altered conscious level, papilloedema and immunodeficiency.

Cerebrospinal fluid (CSF) should be analysed within an hour of collection. If there is a delay, it should be stored between 4 - 8°C.

CSF analysis	**Minimum Volume**
Microscopy and stain (Indian ink and Ziehl Neelsen)	1ml
Biochemistry	1ml
Culture and sensitivity (aerobic and anaerobic)	2ml
Latex agglutination test: *S. pneumoniae*, group B streptococcus, *H. influenzae* type B, *N. meningitidis* group A, B, C, Y and W135, *E.Coli* K1	1ml

CSF analysis	Minimum Volume
Viral: PCR and /or serology Herpes simplex type 1 & 2, varicella zoster virus, Japanese B encephalitis virus, Nipah virus, Enterovirus	3ml
Parasite PCR *Toxoplasma gondii*	3mls
Mycobacterium PCR and culture	10mls
Fungal antigen and culture *Aspergillus fumigatus, Cryptococcus neoformans*	3mls

The results of the bacterial antigen testing should be interpreted with respect to the microscopy and culture results. A diagnosis of bacterial infection based on antigen testing alone is not recommended.

Abnormalities of CSF in various CNS infections:

	Normal	Bacterial Meningitis	Viral Meningitis/ Encephalitis	TB Meningitis	Fungal Meningitis
Pressure (cmH2O)	10 - 20	↑↑	N or ↑	↑	↑
Appearance	Clear	Turbid	Clear	Fibrin web	Clear or Turbid
Protein (g/L)	< 0.45	↑↑	N or ↑	↑↑	↑
Glucose (mmol/L)	2.5 - 3.5	↓↓	N or ↓	↓	↓
CSF:serum glucose ratio	0.4 - 0.5	< 0.4	< 0.6	< 0.5	< 0.5
Lactate (mmols/L)	< 2.9	↑↑	N	↑	↑↑
Cell count/mm^3 (predominant cell type)	0 - 5 lymphocytes & monocytes	> 1000 polymorphs	10 - 1000 polymorphs & mononuclear cells	10 - 1000 lymphocytes	10 - 500 lymphocytes

Non-infective causes may have similar biochemical findings as infective causes. Partial treatment with antibiotics may alter CSF parameters.

The diagnosis of CNS infection in the presence of CNS shunts and drains is largely clinical. Analysis of CSF taken may be suggestive of infection if the cell count > 15/mm^3, CSF:serum glucose < 0.5 or WBC:RBC ratio is less than 1:100. Cell count index (ratio of WBC:RBC in CSF to WBC:RBC in blood) > 1 has also been used as an indicator of infection. A positive CSF culture may represent contaminant and clinical correlation is needed.

Urine specimen

Urine collection must be taken under aseptic technique to minimise the degree of bacterial contamination. The sample should be sent within 2 hours of collection since bacteria will continue to proliferate. Urine samples not sent immediately should be stored at 4°C.

If the patient needs catheterisation, discard the first few mls of urine and collect the rest in the sterile container. If the patient is already catheterised, clamp the catheter and clean the sampling port with 70% alcohol and collect 10 ml sample of urine. Do not take urine samples from the drainage bag due to high risk of bacterial overgrowth leading to false positive results. In and out catheterisation for urine samples in an uncatheterised patient can be done.

Most cases of urinary tract infection (UTI) can be diagnosed using the criteria below. Pyuria in the absence of signs and symptoms in a person with bacteriuria should not be interpreted as symptomatic infection or as an indication for antimicrobial therapy.

	Symptom	Bacteriuria cfu/ml	Pyuria WBC/mm^3	No. of species	Nitirite	Comments
With catheter	Present	≥10^5 in uncomplicated UTI ≥10^4 in complicated UTI ≥10^3 in pregnant women	Pyuria is common in patients with catheter. Its level has no predictive value.	≤ 2	not detected	Treat as UTI. Replace catheter if in place for > 7 days.
	Absent	Routine urine culture in asymptomatic catheterised patients is not recommended. Significant asymptomatic bacteriuria: - a single specimen ≥10^5 cfu/ml - specimen collected by in and out catheter ≥10^2 cfu/ml.				Do not treat bacteriuria except in - Pregnancy - Prior to genitourinary manipulation
Without catheter	Present	≥10^3 in pregnant women and acute uncomplicated cystitis in women ≥10^4 in acute uncomplicated pyelonephritis in women. ≥10^4 in complicated UTI in men ≥10^5 in complicated UTI in women	>10	≤ 2	detected (Only positive in nitrite producing bacteria e.g. *E. coli, Serratia spp, Klebsiella spp* and *Proteus spp*)	Treat as UTI
	Absent	Significant asymptomatic bacteriuria if 2 consecutive MSU grows ≥10^5 cfu/ml of the same bacterial species in women and ≥10^3 cfu/ml in men.				Do not treat bacteriuria except in - Pregnancy - Prior to genitourinary manipulation

For definition of complicated and uncomplicated UTI refer to the chapter on genitourinary tract infection.

Peritoneal fluid specimen

Analysis of peritoneal fluid obtained through paracentesis should be carried out to determine if there is presence of ascitic fluid infection in a patient with ascites and in whom intra-abdominal sepsis is suspected. The fluid should be evaluated for glucose, protein, lactate dehydrogenase (LDH), cell count, Gram stain, and aerobic and anaerobic cultures. Routine intraoperative peritoneal fluid culture in acute abdomen e.g. perforated viscus is controversial.

Classification of ascitic fluid infection in relation to polymorphs cell count and bacterial culture

	Polymorphs count (/mm^3)	**Bacterial culture**	**Treatment**	**Note**
Spontaneous bacterial peritonitis (SBP)	≥ 250	Positive (usually 1 type of organism)	Need antibiotics	In advanced cirrhosis of liver
Culture negative neutrocytic ascites	≥ 250	Negative	Treat as SBP	Causes include: prior antibiotics, peritoneal carcinomatosis, pancreatitis, tuberculous peritonitis
Monomicrobial non-neutrocytic bacteriascites	≤ 250	Positive (1 type of organism)		If asymptomatic, do not treat with antibiotics. Repeat paracentesis. Treat as SBP in presence of sepsis.
Polymicrobial bacteriascites	< 250	Positive (polymicrobial)	No antibiotics	Usually as a result of inadvertent puncture of the intestines during paracentesis.
Secondary bacterial peritonitis	≥ 250	Positive (polymicrobial)	Need antibiotics	

For definition of peritonitis, refer to the chapter on peritonitis.

Secondary bacterial peritonitis should be considered in patients diagnosed with SBP who display persistent symptoms, increasing polymorphs, or a persistently positive ascitic fluid culture despite appropriate antibiotic therapy for 48 hours.

Other characteristics of peritoneal fluid in ascitic fluid infection:

1. Cell count:
   Leucocytes > 500/ml or absolute neutrophils > 250/ml suggests infection. Polymorphonuclear cells and lymphocytes are predominantly seen in bacterial and tuberculous peritonitis respectively. Secondary peritonitis should be suspected if leucocytes are > 10,000/ml

2. Protein level
   Protein levels < 1 g/dL is usually seen in spontaneous peritonitis while levels > 1 g/dL in secondary peritonitis. In tuberculous peritonitis, protein level is typically > 2.5 g/dL.

3. Serum albumin-ascitic fluid albumin gradient
   In tuberculous peritonitis, the gradient is usually < 1.1 g/dL.

4. Glucose levels < 2.7 mmol/L is suggestive of secondary peritonitis.

5. Increased LDH > 225 IU/ml (> upper limit of normal serum) is suggestive of secondary peritonitis. In tuberculous peritonitis, LDH level is usually > 90 IU/ml.

6. Gram stain, culture and sensitivity
   The yield for Gram stain and acid-fast stain is relatively poor in peritoneal fluid. Inoculating peritoneal fluid into blood culture bottles at bedside has been shown to improve sensitivity.

Stool specimen

At least 5 ml of diarrheal stool per rectal or per stoma is collected in a clean leak proof container. The specimen should be transported to the laboratory and processed within 2 hours after collection. Culture of a single stool specimen has a sensitivity of > 95% for detection of the enteric bacterial pathogen.

Acute infectious diarrhea is most often a foodborne or waterborne disease. The causes include viral, bacterial and parasitic pathogens.

Bacteria	Salmonella, Campylobacter, Shigella, *Vibrio cholera*, Yersinia, Listeria, enterotoxigenic *E. coli*, Aeromonas *C. difficile* if recent antibiotic therapy
Protozoal	Cryptosporidium, *Giardia lambia*, Cyclospora, *Entamoeba histolytica*
Virus	Novovirus, rotavirus, enteric adenovirus, astrovirus

Stool culture is not routine in all patients presenting with diarrhea unless immunocompromised, elderly, those with underlying inflammatory bowel disease and with severe or bloody diarrhea. A negative culture for Salmonella, Campylobacter and Shigella usually rules out infection by these organisms as excretion of these pathogens are continuous and repeat specimens are not required.

Stool cultures should not be performed for patients who develop new onset of diarrhea while in hospital as it is likely to be due to antimicrobial therapy. In such cases stools should be sent for *C. difficile* toxin assay instead.

Stool samples for ova and parasites are only recommended in patients with persistent or bloody diarrhea or during waterborne outbreaks. Three specimens should be sent on consecutive days since parasite excretion may be intermittent in contrast to bacterial pathogens.

Clostridium difficile toxin detection falls into two categories of laboratory tests: organism detection assay and toxin assay [enterotoxin (toxin A) and cytotoxin (toxin B)]. Toxin assays available are cytotoxicity assay, enzyme immunoassay (EIA) and PCR. EIA is the preferred diagnostic assay in most clinical laboratories because the technique is relatively simple, inexpensive with results available within 24 hours. However, because of high false negative rates, three consecutive samples are recommended. Positive organism detection without toxin detection does not require treatment because this represents colonisation.

Wound swabs

Wound infections should be diagnosed clinically. Routine cultures of wounds are not indicated unless there are clinical signs of infection. Culturing uninfected wounds may only be used as part of an infection control surveillance protocol.

Tissue specimens obtained from biopsy, ulcer curettage or aspiration are preferable to wound swabs. Wound swabs should be obtained only from viable infected tissue and not from necrotic tissue, eschar or wound debris.

To obtain wound swabs, clean the wound with sterile saline to irrigate purulent debris. Moisten the swab with sterile saline to increase the adherence of bacteria. Rotate the swab while moving it across the entire wound in a zigzag manner. Alternatively Levine's technique can be used where one rotates the swab over $1cm^2$ of the cleansed wound exerting enough pressure to express exudates from within the tissue. Promptly send the swabs obtained to the lab in an appropriate transport media for both aerobic and anaerobic culture.

Bibliography:

1. European Handbook of neurological management 2nd Edition 2011
2. Guidelines on urological infections by European Association of Urology 2011
3. *World Diabetes*: New insights in diabetic foot infections 2011; 2(2): 24-32
4. Clinical Microbiology Procedures Handbook 3rd Edition 2010
5. Wound watch: Three techniques for collecting wound specimen. Jan/Feb 2008 Vol 4 No.1
6. *N Engl J Med* 2002; 346: 1971-7
7. *Hepatology* 1984; 4: 447-450

COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (CAP) is associated with significant morbidity and mortality, particularly in the elderly. 10% of patients who are admitted to the hospital with a diagnosis of CAP will require management in the ICU. The mortality for severe CAP is between 20% to 50%.

Aetiologic pathogens remain unidentified in up to 50% of cases. Empirical therapy should be started after considering patients' risk factors for certain organisms e.g. patients with chronic lung disease are at higher risk of *Pseudomonas aeruginosa* pneumonia.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
S. pneumoniae *H. influenzae* *K. pneumoniae* *M. pneumoniae* *L. pneumophilia* *C. pneumoniae*	IV Amoxicillin/ Clavulanate 1.2g q8h X 5-7 days *PLUS* IV Azithromycin 500mg q24h X 3-5 days	IV Ceftriaxone 2g q24h X 5-7 days *PLUS* IV Azithromycin 500mg q24h X 3-5 days *OR* IV Levofloxacin 750 mg q24h X 5-7 days	The indiscriminate use of 3rd generation cephalosporins may promote the emergence of ESBL producers. Duration of treatment for confirmed atypical infection: 1. Mycoplasma: Azithromycin 5 days Levofloxacin 7 days 2. Chlamydia: Azithromycin 7-10 days. Consider doxycycline if not responding. 3. Legionella: Azithromycin: immunocompetent 7-10 days, immunocompromised up to 3 weeks

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
S. aureus (MSSA)	*PLUS OPTIONAL* IV Cloxacillin 2g q4-6h X 10-14 days		Risk factors (MSSA): 1. ESRF 2. IVDUs 3. Prior antibiotics use especially quinolones 4. Prior influenza Suspect MSSA pneumonia in the presence of cavitary infiltrates without risk factors for anaerobic aspiration.
Community-acquired MRSA (CA-MRSA)	IV Vancomycin 15-20mg/kg q12h X 10-14 days	IV Linezolid 600mg q12h X 10-14 days	Colonisation with CA-MRSA predisposes to pneumonia. Risk Factors for colonisation: 1. Contact sports 2. IVDUs and homosexuals 3. Living in crowded unsanitary conditions eg prison, military barracks 4. Post influenza For loading dose and monitoring of vancomycin refer to **Appendix B.**

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
P. aeruginosa	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8-12h *PLUS* *OPTIONAL* IV Amikacin 15mg/kg/day X 3-5 days OR IV Ciprofloxacin 400mg q8h X 7 days	IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h *OR* IV Doripenem 500mg q8h *PLUS* *OPTIONAL* IV Amikacin 15mg/kg/day X 3-5 days OR IV Ciprofloxacin 400mg q8h X 7 days	Risk factors are severe structural lung disease (e.g. bronchiectasis), COPD, recent antibiotic therapy or hospitalisation. Ceftazidime is not recommended for empirical use because it is the main offender in promoting rapid selection of resistant organism. However if *P. aeruginosa* is sensitive to ceftazidime, consider de-escalation. Dual therapy may be considered in : 1. neutropenic patients 2. CAP with bacteraemia 3. septic shock In confirmed *P. aeruginosa* pneumonia, treat for 10-14 days.
Burkholderia pseudomallei	Refer to chapter on Melioidosis		Risks factors: diabetes mellitus, chronic renal failure, chronic lung disease.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pneumocystis carinii (*Pneumocystis jiroveci*)	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q8h x 21 days	IV Pentamidine 4mg/kg/day x 21 days	Prednisolone should be given 15-30 min before antimicrobials. PO Prednisolone 40mg q12h x 5days, then 40mg q24h x 5days, then 20mg q24h x 11days Patients at risk : 1. HIV infection with CD4+ cells < 200/μL 2. HIV infection with other opportunistic infections e.g. oral thrush 3. Long term immunosuppressive or chemotherapy 4. Primary immunodeficiencies
Viral pneumonias			
Influenza A (pandemic H1N1, seasonal H3N2, avian influenza) Influenza B Varicella zoster Herpes simplex Parainfluenza, RSV, adenovirus, SARS, hantavirus	T. Oseltamivir 75mg q12h x 5 days IV Acyclovir 500mg q8h x 7 days No antiviral of proven value		Oseltamivir 150mg q12h for 10 days should be considered in the critically ill.

Patients with CAP should be treated for a minimum of 5 days, be afebrile for 48 - 72 hours, and have no more than 1 CAP associated sign of clinical instability (temperature > 37.8ºC, heart rate > 100, respiratory rate > 24, systolic pressure < 90mmHg, S_aO_2 < 90%, or P_aO_2 < 60mmHg) before discontinuation of therapy.

A longer duration of therapy may be needed if initial therapy is not active against the identified pathogen or if complicated by extrapulmonary infection, such as meningitis or endocarditis.

If there is no response, consider other possible diagnosis e.g. congestive heart failure, pulmonary embolism, neoplasm, sarcoidosis, drug reaction, pulmonary haemorrhage and empyema. Also consider other causative micro-organisms e.g. mycobacteria, fungi and viruses.

Bibliography:

1. WHO Guidelines for Pharmacological Management of Pandemic Influnza A (H1N1) 2009 and other Influenza Viruses. Revised February 2010
2. *Thorax* 2009; 64 Suppl 3: iii
3. *Clin Infect Dis* 2007; 44 Suppl 2: S27
4. *Clin Infect Dis* 2005; 41(Supplement 4): S269-S272

ASPIRATION PNEUMONIA

The usual causative organisms in aspiration pneumonia are those that colonise the oropharynx. Risk factors for aspiration are conditions that suppress cough and mucociliary clearance. In community-acquired cases, oral anaerobes are the predominant organisms related to poor dentition or oral care and periodontal disease. Hospitalised and institutionalised patients are more likely to have oropharyngeal colonisation with Gram-negative enteric bacilli and *Staphylococcus aureus*. Antimicrobials are not indicated in aspiration without evidence of infection.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Community-acquired			
Oral anaerobes *S. pneumoniae* *H. influenzae* *S. aureus* Enterobacteriaceae *M. catarrhalis*	IV Amoxicillin/ Clavulanate 1.2g q8h	IV Ceftriaxone 2g q24h	Oral anaerobes are sensitive to all ß-lactams. Additional enteric anaerobic (*Bacteroides fragilis*) coverage is not needed. Treat for 7-10 days in patients who respond promptly or longer if complicated with lung abscess or empyema.
Healthcare-associated			
Gram-negative bacilli *P. aeruginosa* *S. aureus* Anaerobes	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8-12h *PLUS* IV Metronidazole 500 mg q8h	IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h	Treat for 7-14 days or longer if complicated with lung abscess or empyema.

Bibliography:

1. *Clin Infect Dis* 2007; 44 Suppl 2: S27

LUNG ABSCESS

Lung abscess is defined as necrosis of the pulmonary parenchyma caused by microbial infection. Common causes include:

i. aspiration pneumonia
ii. severe necrotising pneumonia due to *S. aureus* or *K. pneumoniae*
iii. septic emboli from right sided endocarditis (tricuspid valve endocarditis)
iv. septic thrombophlebitis of internal jugular veins (Lemierre syndrome)

Attempts should be made to identify the causal organism. Bronchoscopy or fine needle aspiration may be required. Drainage of the abscess via a percutaneous catheter is recommended. Antibiotic therapy is generally continued for 4 to 6 weeks.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Secondary to aspiration pneumonia / Lemierre syndrome			
Anaerobes: Peptostreptococci *Fusobacterium spp* Prevotella Bacteroides (usually not *Bacteroides fragilis*) *S. aureus* *E. coli* *K. pneumoniae* *P. aeruginosa* *S. milleri* *S. pneumoniae* *H. Influenzae*	IV Clindamycin 600mg q8h *PLUS* IV Ceftriaxone 2g q24h *OR* IV Ampicillin/ Sulbactam 3g 6qh	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Meropenem 1g q8h *OR* IV Imipenem 500mg 6qh	Use **preferred** therapy in community-acquired or Lemierre syndrome and **alternative** therapy in healthcare-associated infection.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Secondary to tricuspid valve endocarditis			
Methicillin-sensitive *S. aureus* Methicillin-resistant *S. aureus*	Refer to chapter on Infective Endocarditis		
Others			
Burkholderia pseudomallei	Refer to chapter on Melioidosis		

Bibliography:

1. *Thorax* 2010; 65 Suppl 2

HEALTHCARE-ASSOCIATED PNEUMONIA

Healthcare-associated pneumonia (HCAP) is defined as pneumonia in any patient who has been admitted to an acute care hospital for ≥ 2 days of the preceding 90 days; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy within the past 30 days; or attended a hospital or haemodialysis clinic. Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs 48 hours or more after hospitalisation while ventilator-associated pneumonia (VAP) is pneumonia that occurs after 48 hours following intubation.

The timing of HCAP is an important risk factor for pathogens and outcomes in patients with HAP and VAP. Early-onset pneumonia (< 5 days) have a better prognosis as the infecting micro-organisms are more likely to be antibiotic-sensitive than late onset pneumonia (≥ 5 days).

Risk factors for multidrug-resistant (MDR) infections are:

1. Prolonged hospital stay (≥ 5 days)
2. Previous hospitalisation of > 2 days within past 90 days
3. Was on antibiotics within past 90 days, especially broad-spectrum antibiotics
4. Antibiotic resistance in the healthcare setting
5. Admission from long-term care institution
6. Chronic renal dialysis within past 30 days
7. Poor underlying condition
8. Presence of chronic wounds
9. Immunocompromised or neutropenic patient
10. Presence of invasive catheters e.g. central venous catheters

It is now recognised that MDR organisms are increasing in frequency. The prevalence of these organisms varies from unit to unit hence guidelines will not replace auditing of local microbiological data. Occasionally the causative organisms in pneumonia may be polymicrobial.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical treatment in patients without risk factors for MDR pathogens			
S. pneumoniae *H. influenzae* *S. aureus* *E. coli* *K. pneumoniae*	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Cefuroxime 1.5g q8h X 5-7 days	IV Ceftriaxone 2g q24h X 5-7days	*S. aureus* is more common in diabetes mellitus, head trauma.
P. aeruginosa	IV Piperacillin/ Tazobactam 4.5g q6h X 10-14 days	IV Cefepime 2g q8-12h X 10-14 days	Consider in patients with chronic lung disease.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical treatment in patients with risk factors for MDR pathogens			
P. aeruginosa *K. pneumoniae*	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8-12h *PLUS OPTIONAL*	IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h *PLUS OPTIONAL*	Consider the **alternative** regime if patient is haemodynamically unstable.
Acinetobacter spp	IV Cefoperazone/ Sulbactam 4g q6h *OR* IV Ampicillin/ Sulbactam 3g q3h *PLUS OPTIONAL*	IV Polymyxin E 3 million units q8h *PLUS OPTIONAL*	Sulbactam component of 8g/day is required.
Methicillin-resistant *S. aureus*	IV Vancomycin 15-20mg/kg q12h	IV Linezolid 600mg q12h	For loading dose and monitoring of vancomycin refer to **Appendix B**.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
P. aeruginosa	IV Ceftazidime 2g q8h *OR* IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8-12h X 10-14 days *PLUS OPTIONAL* IV Amikacin 15mg/kg/day X 3-5 days *OR* IV Ciprofloxacin 400mg q8h X 7 days	IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h X 10-14 days *PLUS OPTIONAL* IV Amikacin 15mg/kg/day X 3-5 days *OR* IV Ciprofloxacin 400mg q8h X 7 days	Use the **alternative** regime in gp 1 ß-lactamase. Use IV polymyxin in carbapenem-resistant *P. aeruginosa*. Combination therapy for pseudomonal infection has not been shown to be superior to monotherapy. Dual therapy may be considered in 1. neutropenic patients 2. pneumonia with bacteraemia 3. septic shock
Acinetobacter spp	IV Cefoperazone/ Sulbactam 4g q6h *OR* IV Ampicillin/ Sulbactam 3g q3h X 10-14 days	IV Polymyxin E 3 million units q8h X 10-14 days	Sulbactam component of 8g/day is required.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
K. pneumoniae (ESBL)	IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h *OR* IV Doripenem 500mg q8h X 7-10 days		The evidence for use of ertapenem in the critically ill is limited at present.
Methicillin-resistant *S. aureus*	IV Vancomycin 15-20mg/kg q12h X 10 - 14 days	IV Linezolid 600mg q12h X 10-14 days	For loading dose and monitoring of vancomycin refer to **Appendix B**. Consider linezolid in necrotising pneumonia.
Stenotrophomonas maltophilia	IV Trimetoprim/ Sulfamethoxazole 5mg/kg (TMP component) q8h X 10-14 days		Carbepenem therapy is associated with the emergence of this organism.

Bibliography:

1. *Clin Infect Dis* 2011: 52: 285-322
2. *Clin Infect Dis* 2010; 51 (Suppl 1): S42-47
3. *J Infection* 2008: 56; 432-436
4. *Scand J Infect* Dis. 2007; 39(1): 38-43.
5. *Curr Anaes and Crit Care* 2005; 16: 209-219
6. *Am J Respir Crit Care Med* 2005; 171: 388-416

GENITOURINARY TRACT INFECTION

Urinary tract infections (UTI) is the most common genitourinary tract infection seen in the critically ill patient. It can manifest from asymptomatic bacteriuria to severe sepsis. Acute pyelonephritis is the commonest form of UTI. Mortality associated with septic shock secondary to urosepsis is substantially lower compared to other sites of infection. Sterile pyuria or asymptomatic bacteriuria is common in catheterised patients and does not warrant treatment. However catheter-associated urinary tract infection (CAUTI) is not uncommon and should be treated.

For purposes of practicality and differences in clinical approach, UTIs are classified into uncomplicated or complicated. Uncomplicated UTI is restricted to UTI in a non-pregnant immunocompetent woman with no anatomical or functional abnormality of the urinary tract.

A complicated UTI is associated with significant bacteriuria in an underlying condition that increases the risk of treatment failure, which includes:

1. presence of indwelling catheter, stents or nephrostomy tubes
2. functional and/or anatomical abnormalities
   e.g. neurogenic bladder, vesicoureteric reflux
3. obstructive uropathy
4. renal failure
5. pregnancy
6. diabetes mellitus
7. immunosuppressed states e.g. renal transplant,
   febrile neutropenia, HIV
8. UTI caused by drug resistant pathogens
9. UTI in males (except young males with exclusively lower
   UTI symptoms)

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Acute Uncomplicated Pyelonephritis			
E. coli *Klebsiella spp* *P. mirabilis*	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/ Sulbactam 3g q6h X 7-14 days	IV Cefuroxime 1.5g q8h *OR* IV Ceftriaxone 2g q24h X 7-14 days	

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Acute Complicated Pyelonephritis / CAUTI			
	Antibiotic naïve		
E. coli *Klebsiella spp* *P. mirabilis*	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/ Sulbactam 3g q6h X 14-21 days	IV Cefuroxime 1.5g q8h *OR* IV Ceftriaxone 2g q24h X 14-21 days	Do not use cephalosporin for suspected enterococcal infection. Use of ciprofloxacin is associated with increased incidence of resistant strains. In CAUTI: 1. Catheters should be removed or replaced. 2. Duration of treatment is 7 days if prompt resolution of symptoms or 10-14 days in delayed response whether still catheterised or not Obstructive uropathy should be sought and relieved. Switch to oral therapy when possible to complete course.
	Previous antibiotic exposure		
E. coli *Klebsiella spp* *P. mirabilis* *P. aeruginosa* *Enterobacter spp* Enterococci ESBL producing Enterobacteriacae	IV Piperacillin/ Tazobactam 4.5g q8h X 14-21 days	IV Cefepime 2g q8-12h *OR* IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h X 14-21 days	
Candida albicans	IV Fluconazole 800mg stat then 400mg q24h X 14-21 days		

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Renal Abscess (intrarenal or perinephric)			
Methicillin-sensitive *S. aureus*	IV Cloxacillin 2g q4-6h		Consider image-guided aspiration or surgical drainage of abscess.
Methicillin-resistant *S. aureus*	IV Vancomycin 15-20mg/kg q12h	IV Linezolid 600mg q12h	Duration of therapy should be prolonged.
Enterobacteriaceae	Treat as acute complicated pyelonephritis		For loading dose and monitoring of vancomycin refer to **Appendix B**.
Pelvic Inflammatory Disease/ Tuboovarian Abscess			
Bacteroides fragilis *G. vaginalis* *H. influenzae* Enterobacteriaceae *N. gonorrhoeae* *C. trachomatis*	IV Ceftriaxone 2g q24h *PLUS* IV Metronidazole 500mg q8h X 7 days *PLUS* PO Doxycycline 100mg q12h X 14 days	IV Ampicillin/ Sulbactam 3g q6h X 7 days *PLUS* PO Doxycycline 100mg q12h X 14 days	There is emerging evidence on the use of azithromycin in mild to moderate PID.

Bibliography:

1. The Sanford Guide to Antimicrobial Therapy 2011: 30-31
2. Guidelines on urological infections by European Association of Urology 2011
3. *Clin Infect Dis* 2011; 52(5): e103
4. *Clin Infect Dis* 2010; 50: 625

ACUTE INFECTIVE DIARRHOEA

Acute infective diarrhoea is usually self-limiting and does not require antimicrobials. Patients admitted to the ICU are usually in shock with systemic involvement and therefore, empirical antimicrobials need to be started.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy (community acquired) : non bloody diarrhoea			
Salmonella typhi and non *typhi* *Vibrio cholerae* Enterotoxigenic *E.coli* (ETEC)	IV Ceftriaxone 2g q24h X 7-10 days	IV Ciprofloxacin 400mg q12h X 7-10 days *PLUS* PO Azithromycin 1g single dose *OR* PO Doxycycline 300mg single dose	Addition of azithromycin/ doxycycline is for the coverage of *Vibrio cholerae* as ciprofloxacin resistance is increasing. If ETEC is isolated, stop antibiotics.
Empirical therapy (community acquired) : bloody diarrhoea			
Shigella spp Enterohaemorrhagic *E. coli* 0157 (EHEC)	IV Ceftriaxone 2g q24h X 3 days	IV Ciprofloxacin 400mg q12h X 3 days	If *E.coli* 0157 (commonest strain), is isolated, stop antibiotics and observe for haemolytic uraemic syndrome (HUS).

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific: Community-acquired			
Shigella spp	IV Ceftriaxone 2g q24h X 3 days	IV Ciprofloxacin 400mg q12h *OR* IV Azithromycin 500mg q24h X 3 days	If *S. dysenteriae* type 1 is isolated or in patients with HIV, treat for 5 - 7 days.
Vibrio cholerae	PO Azithromycin 1g *OR* PO Doxycycline 300mg X 1 dose	PO Ciprofloxacin 500mg q12h X 3 days	
Salmonella typhi and non-*typhi*	IV Ceftriaxone 2g q24h X 7-10 days	IV Ciprofloxacin 400mg q12h X 7-10 days	

***Clostridium difficile*-associated disease**

Clostridium difficile-associated disease (CDAD) is suspected when patients present with watery diarrhoea, even for a day, associated with fever (T > 38.5ºC) and abdominal pain. CDAD rarely presents as ileus. Diagnosis is made by the detection of *C. difficile* toxin in the stools. Colonoscopy may aid diagnosis should CDAD be suspected when laboratory confirmation is delayed or negative, or when presentation is atypical. Risk factors are hospitalisation, exposure to antibiotics (mainly clindamycin, cephalosporins, quinolones and penicillin) and advanced age. Offending antibiotics should be discontinued if possible.

Relapse occurs in up to 27% of cases, typically between 3 days to 3 weeks after treatment is discontinued. Metronidazole should not be used after the first recurrence.

Consider infectious disease consultation in cases of relapse.

Severity of illness	Antimicrobials	Notes
Mild to moderate	PO Metronidazole 400mg q8h X 10-14 days	Severity: 1. mild to moderate: TWC < 15 and creat < 1.5x baseline
Severe	PO Vancomycin 125 mg q6h X 10-14 days	2. severe: TWC > 15 and creat > 1.5x baseline
Severe complicated	PO Vancomycin 500 mg q6h *PLUS* IV Metronidazole 500mg q8h	3. severe complicated: presence of shock, ileus or megacolon IV vancomycin is not effective. IV formulation can be given orally. In complete ileus, consider concurrent rectal vancomycin 500mg q6h. Fulminant colitis and toxic megacolon may require operative intervention. Duration of treatment depends on clinical response.

Bibliography:

1. *Infect Control Hosp Epidemiol* 2010; 31: 431-455
2. Cochrane Database Syst Rev. 2007
3. *N Engl J Med* 2004; 350(1): 38
4. *Clin Infect Dis* 2001; 32(3): 331

ACUTE INFECTIVE PANCREATITIS

Patients with severe acute pancreatitis who develop infection tend to have more than 30% necrosis of the pancreas. Infection usually occurs late (after 10 days) in the clinical course of the disease. The important organisms causing infection in necrotising pancreatitis are predominantly gut-derived, and the majority are monomicrobial.

The diagnosis of infective pancreatitis is a combination of clinical and laboratory investigations (persistent leucocytosis, CRP > 150 mg/L after 48 hrs of symptom onset). To further define infection, CT/US guided aspiration with Gram-staining and cultures is recommended.

There is disparate opinion as to the use of prophylactic antimicrobial in severe necrotising pancreatitis. The prophylactic use should be considered if the patient has severe necrosis (> 30% confirmed on CT scan) with evidence of multi-organ failure and high severity illness score.

The antibiotics for prophylaxis should penetrate necrotic tissue effectively. The duration of prophylaxis is 7-14 days with clinical reassessment of risk-benefit to be made on day 7. The prophylactic antibiotic of choice is similar to that used in the treatment of infected pancreatitis. There is no indication for the use of prophylactic antifungal.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Enterobacteriaceae *(E. coli, Klebsiella spp. Proteus spp.) Enterococcus spp Bacteroides spp*	IV Piperacillin/ Tazobactam 4.5g q6h	IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h	Infected pancreatic necrosis is an indication for surgical or radiological-guided drainage. Duration of treatment is guided by repeated clinical and serial radiological assessments.
Candida albicans Candida non albicans	IV Fluconazole 800mg (loading dose) followed by 400mg q24h *OR* IV Amphotericin B 0.6-1mg/kg/day	IV Caspofungin 70mg (loading dose) followed by 50mg q24h *OR* IV Anidulafungin loading dose 200mg followed by 100mg q24h	The risk of fungal infection in severe pancreatitis is high and empirical treatment should be considered early if no improvement despite broad spectrum antimicrobials. Consider amphotericin B if patient has had recent azole exposure in the past 3 months. Echinocandins (or lipid-based amphotericin B) to be considered in patients with recent azole exposure and renal dysfunction

Bibliography:

1. *Am J Gastroenterol* 2008; 103(1): 104
2. *Am J Gastroenterol* 2006; 101(10): 2379
3. *Gastroenterology* 2007; 132(5): 2022
4. Cochrane Database Syst Re. 2006.

BILIARY SEPSIS

Acute cholangitis can be a life-threatening infection secondary to the obstruction of common bile duct by gall stones or strictures. Besides antimicrobial therapy, prompt decompression and drainage of the biliary tract need to be considered.

Acute cholecystitis is primarily an inflammatory process and secondary infection of the gall bladder can occur as a result of cystic duct obstruction and bile stasis. Antimicrobial therapy is instituted in the presence of leukocytosis or fever, and radiologic findings of air in the gallbladder or gall bladder wall. Antimicrobials are also recommended in patients of advanced age, diabetics or immunocompromised.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Enterobacteriaceae (*E. coli*, *Klebsiella spp*, *Enterobacter spp*) Enterococci *P. aeruginosa* Anaerobes (*Bacteroides fragilis*, *C. perfringens*)	IV Cefoperazone 2g 12qh *PLUS* IV Metronidazole 500mg 8qh X 7-10 days	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8-12h PLUS IV Metronidazole 500mg q8h *OR* IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h *OR* IV Doripenem 500mg q8h X 7-10 days	Consider the **alternative** regime in patients with recent ERCP, presence of stents or entero-biliary surgery. Consider enterococcal cover in: immunocompromised (solid organ transplant or steroid therapy), valvular heart disease, intravascular prosthetic devices or previous antimicrobial use. Ceftriaxone may increase biliary sludging.

Bibliography:

1. *Clin Infect Dis* 2010; 50(2): 133-64

LIVER ABSCESS

Liver abscess is classified by aetiology into pyogenic, amoebic and fungal abscess. Pyogenic abscess is the most common and may occur following spread through the biliary tree, by extension of adjacent infection or following instrumentation e.g. chemoembolisation or biliary sphincterotomy. Invasive *Klebsiella pneumoniae* liver abscess syndrome (KLAS) is a community-acquired primary liver abscess that may have metastatic manifestations (endophthalmitis, meningitis, brain abscess). Abscess caused by *Burkholderia pseudomallei* should be considered in patients who present with shock.

Amoebic liver abscess may be seen in patients who are from or have visited endemic areas. Serological test is positive for most patients with amoebic liver abscess. Fungal liver abscess is usually due to *Candida albicans* and occurs in patients with immunosuppression.

Besides antimicrobial therapy, drainage of the abscess need to be considered. Pyogenic liver abscess will require 4-6 weeks of antimicrobial therapy. Amoebic liver abscess will require 7-10 days of antimicrobial therapy followed by a luminal agent for eradication of gut colonisation.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Enterobacteriaceae *(E. coli, Klebsiella pneumoniae)* *S. milleri* *Enterococcus spp* *S. aureus* Anaerobes *(Bacteroides spp, Fusobacterium spp, Actinomyces spp, Clostridium spp)* *Entamoeba histolytica*	**Empirical therapy in the haemodynamically unstable**		Consider carbapenem when melioidosis is suspected. Consider antifungal therapy in immunocompromised or neutropenic patients. Metronidazole is added to cover *Entamoeba histolytica.*
	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8-12h	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h	
	PLUS IV Metronidazole 500mg q8h		
	Empirical therapy in the haemodynamically stable		
	IV Ceftriaxone 2g q24h *PLUS* IV Metronidazole 500mg q8h	IV Piperacillin/ Tazobactam 4.5g q6h *PLUS* IV Metronidazole 500mg q8h	

Bibliography:

1. The Sanford Guide to Antimicrobial Therapy 2011
2. *Clin Infect Dis* 2010; 50: 133-164
3. *Clin Infect Dis* 2007; 45(3): 284

PERITONITIS

In complicated intra-abdominal infections, the infective process extends beyond the organ and causes either localised peritonitis with abscess formation or diffuse peritonitis. Complicated intra-abdominal infections can be classified into:

1. Primary or spontaneous bacterial peritonitis: a diffuse bacterial infection without loss of integrity of the gastrointestinal tract.
2. Secondary peritonitis: acute peritoneal infection resulting from loss of integrity of the gastrointestinal tract or from infected viscera. It may be community-acquired or health care-associated e.g. perforation of the gastrointestinal tract, anastomotic dehiscence.
3. Tertiary peritonitis: persistent or recurrent infection that typically occurs at least 48 hours after apparently adequate management of primary or secondary peritonitis.

Source control to eradicate focus of infection and prevent ongoing microbial contamination is fundamental to the management of patients with complicated intra-abdominal infections. Selection of empiric antimicrobial therapy depends mainly on the severity of illness and whether the infection is community-acquired or healthcare-associated.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Spontaneous bacterial peritonitis			
E.coli *Klebsiella spp* *S.pneumoniae* Enterococci	IV Ceftriaxone 2g q24h X 5 days	IV Piperacillin/ Tazobactam 4.5g q6h X 5 days	

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Community-acquired secondary peritonitis			
Enterobacteriaceae (esp. *E. coli)* *Streptococcus milleri* Anaerobes (esp. *Bacteroides fragilis)*	**Mild to moderately ill**		Bowel perforation from penetrating or blunt trauma, repaired within 12h should only be treated with antibiotics for 24h. Antimicrobial therapy is only required for 24h post operatively in: 1. Acute perforations of the stomach, duodenum, proximal jejunum (with absence of antacid therapy or malignancy) when source control is achieved within 24h 2. Acute appendicitis (without evidence of gangrene, perforation, abscess, peritonitis). Use of anti-MRSA or antifungal is not recommended in the absence of evidence of infection by such organisms.
	IV Amoxicillin/ Clavulanate 1.2g q8h X 5-7 days	IV Ceftriaxone 2g q24h *OR* IV Cefoperazone 2g q12h *PLUS* IV Metronidazole 500mg q8h X 5-7 days	
	Severely ill		
	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8-12h *PLUS* IV Metronidazole 500mg q8h X 5-7 days	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h *OR* IV Doripenem 500mg q8h X 5-7 days	

<table>
<tr><th rowspan="2">Common Organisms</th><th colspan="2">Antimicrobials</th><th rowspan="2">Notes</th></tr>
<tr><th>Preferred</th><th>Alternative</th></tr>
<tr><td colspan="4">Healthcare-associated secondary peritonitis and tertiary peritonitis</td></tr>
<tr><td rowspan="4">ESBL–producing enterobacteriaceae
(E. coli, Klebsiella spp)
Enterobacter spp
Proteus spp
P. aeruginosa
Acinetobacter spp
Enterococci
Anaerobes</td><td colspan="2">Risk for ESBL-producing enterobacteriaceae</td><td rowspan="4">Following adequate source control, antimicrobials should be discontinued when there is resolution of fever, normalisation of WBC and return of gastrointestinal function.

Risks of selection of ESBL–producing enterobacteriaceae: prior exposure to 3rd gen. cephalosporins, multiple antibiotics.

Consider enterococcal cover in tertiary peritonitis, previously on cephalosporins, immunocompromised, valvular heart disease or prosthetic intravascular materials.

Consider anti-MRSA in those colonised with MRSA, prior MRSA treatment failure or significant antibiotic exposure.

For loading dose and monitoring of vancomycin refer to Appendix B.

Consider antifungal in severe hospital-acquired infections.</td></tr>
<tr><td>Low</td><td>High</td></tr>
<tr><td>IV Piperacillin/ Tazobactam 4.5g q6h

OR

IV Cefepime 2g q8-12h
PLUS
IV Metronidazole 500mg q8h</td><td>IV Meropenem 1g q8h

OR

IV Imipenem 500mg q6h

OR

IV Doripenem 500mg q8h</td></tr>
<tr><td colspan="2">PLUS OPTIONAL

IV Vancomycin 15-20mg/kg q12h

PLUS OPTIONAL

IV Fluconazole 800mg stat and 400mg q24h</td></tr>
<tr><td>Methicillin-resistant S. aureus

Candida albicans</td><td colspan="2"></td><td></td></tr>
</table>

Bibliography:

1. *World J Emerg Surg* 2011, 6:2 doi: 10.1186/1749-7922-6-2
2. *Clin Infect Dis* 2010; 50: 133-64

CATHETER-RELATED BLOODSTREAM INFECTION

Patients with short term CVC are suspected to have catheter-related infection if they have an acute febrile episode with or without hypotension, hypoperfusion and organ dysfunction in the absence of other identifiable sources of infection.

In patients who are haemodynamically unstable, catheter must be removed. In stable patients catheter may be left in-situ if still needed. However it must be removed when cultures are positive or fever persists with unidentified source of sepsis.

Diagnosing catheter-related bloodstream infection (CRBSI) requires simultaneous blood sampling from the catheter hub and the peripheral blood into appropriately labeled bottles. A definitive diagnosis of CRBSI requires the same organism grown from the blood cultures with either

1. quantitative cultures of blood samples having a ratio of ≥ 3:1 cfu/ml of blood (catheter: peripheral).
2. differential time to positivity (DTP) of at least 2 hours: growth from the catheter hub at least 2 hours earlier than the periphery.

Qualitative culture of catheter tip is not recommended. If catheter tip (5cm length) is cultured, a semi quantitative culture of > 15 cfu or quantitative culture of > 10^2 cfu plus a peripheral blood culture of the same organism confirms the diagnosis of CRBSI.

Presence of catheter site inflammation alone does not always indicate CRBSI and vice versa. This section deals only with CRBSI associated with short-term central venous catheters.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy in the haemodynamically stable			
Methicillin sensitive: Coagulase-negative *S. epidermidis* (CoNS) *S. aureus* Methicillin resistant: *S. aureus* *S. epidermidis*	IV Cloxacillin 2g q6h IV Vancomycin 15-20mg/kg q12h		Empirical therapy should be stopped if cultures are negative. Consider MRSA/MRSE in patients with prosthetic valves or vascular graft, prior antibiotic use, on hemodialysis, prolonged hospital stay, HIV +ve and residence of long term care facilities. For loading dose and monitoring of vancomycin refer to **Appendix B**. IV linezolid should not be used as empirical therapy.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy in the haemodynamically unstable			
Gram-negative bacilli	IV Cefepime 2g q8-12h *OR* IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefoperazone/ Sulbactam 4g q6h *PLUS OPTIONAL*	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h *OR* IV Polymyxin E 3 million units q8h	The choice of antimicrobials depends on the local flora and susceptibility patterns. Consider Gram-negative cover in neutropenia, severe sepsis or patients known to be colonised with such pathogens. Consider MRSA cover in patients with prolonged hospital stay, prior antibiotic use, on dialysis, HIV +ve and residence of long term care facilities. For loading dose and monitoring of vancomycin refer to **Appendix B**. Risk factors for Candida: TPN, femoral line, prolonged use of broad spectrum antibiotics, haematological malignancy or candida colonisation at multiple sites. Echinocandin (or lipid-based amphotericin B) may be considered in patients who have prior exposure to an azole in the last 3 months with renal dysfunction.
MRSA	IV Vancomycin 15-20mg/kg q12h *PLUS OPTIONAL*	*PLUS OPTIONAL*	
Candida spp	IV Fluconazole 800mg stat then 400mg q24h	IV Amphotericin B 0.6-1mg/kg q24h *OR* IV Caspofungin 70mg stat then 50mg q24h *OR* IV Anidulafungin 200mg stat then 100mg q24h	

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
Methicillin sensitive: *CoNS*	IV Cloxacillin 2g q6h X 5-7 days		Infected catheters must be removed. Duration of therapy in complicated infection:
S.aureus	IV Cloxacillin 2g q6h X 14 days		a. endocarditis / suppurative thrombophlebitis 4-6 wks b. osteomyelitis 6-8 wks
Methicillin resistant: *CoNS*	IV Vancomycin 15-20mg/kg q12h X 5-7 days	IV Linezolid 600mg q12h X 5-7 days	For loading dose and monitoring of vancomycin refer to **Appendix B**.
S.aureus	IV Vancomycin 15-20mg/kg q12h X 14 days	IV Linezolid 600mg q12h X 14 days	
Enteroccocus spp Ampicillin sensitive Ampicillin resistant Vancomycin resistant	IV Ampicillin 2g q6h IV Vancomycin 15-20mg/kg q12h IV Linezolid 600mg q12h X 7-14 days	 IV Daptomycin 6mg/kg q24h X 7-14 days	Refer to the above for the duration of treatment in complicated infections.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
Non-ESBL *E. coli* *Klebsiella spp*	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Cefuroxime 1.5g q8h X 7-14 days	IV Ceftriaxone 2g q24h X 7-14 days	Consider in patient with femoral catheters.
ESBL *E. coli* *Klebsiella spp* ESBL or non-ESBL *Enterobacter spp*	IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h *OR* IV Doripenem 500mg q8h X 10-14 days		The evidence for use of ertapenem in the critically ill is limited at present.
Acinetobacter spp	IV Ampicillin/ Sulbactam 3g q3h *OR* IV Cefoperazone/ Sulbactam 4g q6h X10-14 days	IV Polymyxin E 3 million units q8h X 10-14 days	Sulbactam component of 8g/day is required.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
P. aeruginosa	IV Ceftazidime 2g q8h *OR* IV Cefepime 2g q8-12h *OR* IV Piperacillin/ Tazobactam 4.5g q6h X 10-14 days *PLUS OPTIONAL* IV Amikacin 15mg kg/q24h X 3-5 days *OR* IV Ciprofloxacin 400mg q8h X 7 days	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h *OR* IV Doripenem 1g q8h X 10-14 days *PLUS OPTIONAL* IV Amikacin 15mg/kg q24h X 3-5 days *OR* IV Ciprofloxacin 400mg q8h X 7 days	Use the **alternative** regime in gp. 1 ß-lactamase. Use IV polymyxin in carbapenem-resistant *P. aeruginosa*. Dual therapy may be considered in 1. neutropenic patients 2. septic shock
Candida albicans Candida non albicans	IV Fluconazole 800mg stat then 400mg q24h IV Amphotericin B 0.6-1mg/kg q24h	IV Anidulafungin 200mg stat then 100mg q24h *OR* IV Caspofungin 70mg stat then 50mg q24h	Treat for 14 days after last positive blood culture. Consider echinocandins (or lipid-based amphotericin B) in patients with recent azole exposure and renal dysfunction.

Bibliography:

1. *Clin Infect Dis* 2009; 49(1): 1-45

INFECTIVE ENDOCARDITIS

Duke's criteria is widely used for diagnosis of infective endocarditis (IE). Three sets of blood cultures should be obtained prior to initiation of antibiotic therapy. An echocardiogram should be done in all suspected cases. Treatment is guided by presentation, clinical findings, native or prosthetic valves and organism virulence. Indications for surgery include the following: heart failure, uncontrolled infection and large vegetations.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy			
Native valve	IV Benzylpenicillin 3 million units q4h *PLUS* IV Gentamicin 1mg/kg q8h *PLUS OPTIONAL* IV Cloxacillin 2g q4h	IV Cefriaxone 2g q24h *PLUS OPTIONAL* IV Cloxacillin 2g q4h	Consider cloxacillin in intravenous drug users. Benzylpenicillin: 1 million units = 600mg
Prosthetic valve	IV Vancomycin 15-20mg/kg q12h *PLUS* IV Gentamicin 1mg/kg q8h *PLUS* PO Rifampicin 300mg q8h		For loading dose and monitoring of vancomycin refer to **Appendix B**. There is increasing evidence for single daily dose of gentamicin 3mg/kg/day.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
S. viridans *S. bovis* Highly penicillin-susceptible: MIC ≤0.12 µg/ml	IV Benzlpenicillin 3 million units q4h *OR* IV Ceftriaxone 2g q24h X 4 weeks	IV Benzylpenicillin 3 million units q4h *OR* IV Ceftriaxone 2g q24h *PLUS* IV Gentamicin 1mg/kg q8h X 2 weeks	The **alternative** 2-week regime is not recommended for patients age > 65 years old, creatinine clearance < 20ml/min, deafness and known cardiac or extra-cardiac abscesses Duration of treatment in prosthetic valve endocarditis is 6 weeks for **preferred** regime.
S. viridans *S. bovis* Relatively resistant to penicillin: MIC ≥ 0.12 µg/ml	IV Benzylpenicillin 4 million units q4h X 4 weeks *PLUS* IV Gentamicin 1mg/kg q8h X 2 weeks	IV Ceftriaxone 2g q24h X 4 weeks *PLUS* IV Gentamicin 1mg/kg q8h X 2 weeks	Duration of treatment in prosthetic valve endocarditis is 6 weeks

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
S. aureus (Native valve- left side and complicated right sided) (Native valve- uncomplicated right sided)	IV Cloxacillin 2g q4h X 6 weeks *PLUS* IV Gentamicin 1mg/kg q8h X 3-5 days IV Cloxacillin 2g q4h *PLUS* IV Gentamicin 1mg/kg q8h X 2 weeks	If MRSA : IV Vancomycin 15-20mg/kg q12h X 6 weeks *PLUS* IV Gentamicin 1mg/kg q8h X 3-5 days	Uncomplicated right-sided endocarditis: absence of heart failure, extra-pulmonary metastatic infection such as osteomyelitis, aortic or mitral valve involvement, meningitis or infection with MRSA.
S. aureus (Prosthetic valve)	IV Cloxacillin 2g q4h X 6 weeks *PLUS* PO Rifampicin 300mg q8h X 6 weeks *PLUS* IV Gentamicin 1mg/kg q8h X 2 weeks	If MRSA: IV Vancomycin 15-20mg/kg q12h X 6 weeks *PLUS* PO Rifampicin 300mg q8h X 6 weeks *PLUS* IV Gentamicin 1mg/kg q8h X 2 weeks	

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
Enterococcus spp (Ampicillin sensitive) *Enterococcus spp* (Ampicillin resistant)	IV Ampicillin 2g q4h *PLUS* IV Gentamicin 1mg/kg q8h IV Vancomycin 15-20 mg/kg q12h *PLUS* IV Gentamicin 1mg/kg q8h		Duration of treatment: Native valve with symptoms < 3 months - 4 weeks Native valve with symptoms > 3 months - 6 weeks Prosthetic valve is minimum 6 weeks
HACEK *Haemophilus spp* *Actinobacillus actinomycetemcomitans* *Cardiobacterium hominis* *Eikenella corrodens* *Kingella spp*	IV Ampicillin/ Sulbactam 3g q6h X 4 weeks	IV Ceftriaxone 2g q24h X 4 weeks	

Bibliography:

1. *Eur Heart J* 2009; 30: 2369
2. *Circulation* 2005; 111: 3167

CENTRAL NERVOUS SYSTEM INFECTION

The approach to the patient with suspected acute central nervous system infection is early recognition of the disease, performance of rapid diagnostic tests, prompt antimicrobial therapy and adjunctive therapy whenever appropriate.

The choice of empirical antibiotic to treat acute bacterial meningitis is influenced by the patient's age, immune status and predisposing conditions. The antibiotic used in meningitis should have bactericidal action with high concentration of antibiotic in the CSF as the immune activity in the CSF is poor. Current evidence suggests the use of dexamethasone only in pneumococcal meningitis.

There is no specific antimicrobial for most viral encephalitis. However, acyclovir should be initiated in all patients with suspected encephalitis although it is only specific to herpes virus infection.

Limited case series have been reported on the use of intrathecal antibiotics alongside parenteral treatment. The greatest clinical experience is with vancomycin, gentamicin and polymyxin - antibiotics that are known to have poor CNS penetration. Currently there is no antibiotic approved by FDA for intrathecal use.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Acute bacterial meningitis – community-acquired			
S. pneumoniae *N. meningitidis* *H. influenzae* Aerobic Gram-negative bacilli (more common in age > 50, immuno-compromised) *Listeria monocytogenes* (uncommon in Malaysia)	IV Ceftriaxone 2g q12h	IV Cefotaxime 2g q6h	Add IV vancomycin if prevalence of cephalosporin-resistant *S. pneumoniae* is > 2%. Add IV dexamethasone 0.15mg/kg (10mg) q6h X 4 days in pneumococcal meningitis. 1st dose to be given 10-20 min before, or concomitant with the first dose of antibiotic. Omit if antibiotics have been started. Treat Listeria meningitis with IV ampicillin 2g q4h ± IV gentamicin if CSF Gram-stain reveals Gram-positive rods or when confirmed.
	Duration of treatment: *N. meningitidis X 7days* *H. influenzae X 7 days* *S. pneumoniae X 14 days* Aerobic Gram negative bacilli X 21 days *L. monocytogenes* X 21 days or longer if immunocompromised		
Acute bacterial meningitis - Post head injury (base of skull fracture)			
S. pneumoniae *H. influenzae* Group A ß-haemolytic streptococci	IV Ceftriaxone 2g q12h	IV Cefotaxime 2g q6h	

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Acute bacterial meningitis - Penetrating trauma, post neurosurgery, shunts including lumbar catheters			
S. aureus Coagulase-negative staphylococci Aerobic Gram-negative bacilli	IV Ceftriaxone 2g q12h *PLUS* IV Cloxacillin 2g q6h X 14 days	IV Cefepime 2g q8h *OR* IV Meropenem 2g q8h *PLUS* IV Vancomycin 15-20mg/kg q12h X 14 days	Remove infected shunt. Consider the **alternative** regime if at risk for MDR pathogens e.g. prolonged hospital stay, previous broad-spectrum antibiotic. For loading dose and monitoring of vancomycin refer to **Appendix B**.
Acute encephalitis			
Herpes simplex Herpes zoster Arboviruses Flaviviruses	IV Acyclovir 10mg/kg q8h X 14 days No antiviral of proven value		If immunocompromised to treat for 21 days.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess - Haematogenous and contiguous spread			
Streptococci *Bacteroides spp* Enterobacteriaceae *S. aureus*	IV Ceftriaxone 2g q12h *PLUS* IV Metronidazole 500mg q8h	IV Cefotaxime 2g q6h *PLUS* IV Metronidazole 500mg q8h	Contiguous spread can occur from otitis media, mastoiditis and sinusitis which will need surgical drainage. Consider surgical drainage if brain abscess is > 2.5cm. *S. aureus* abscess is rare in the absence of a positive blood culture. Minimum duration of treatment is 4-6 weeks and response is guided by neuro imaging.
Brain abscess - Post surgery / post trauma			
S. aureus Aerobic Gram-negative bacilli	IV Ceftriaxone 2g q12h *PLUS* IV Cloxacillin 2g q4h	IV Cefepime 2g q8h *OR* IV Meropenem 2g q8h *PLUS* IV Vancomycin 15-20mg q12h	Consider surgical drainage if abscess is > 2.5cm. Consider the **alternative** regime if at risk for MDR e.g. prolonged hospital stay, previous broad-spectrum antibiotic use. Minimum duration of treatment is 4-6 weeks and response is guided by neuro imaging. For loading dose and monitoring of vancomycin refer to **Appendix B**.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess - Cyanotic heart disease			
Streptococci (esp. *S. milleri)* *H.influenzae* *S. aureus*	IV Ceftriaxone 2g q12h		Consider surgical drainage if abscess is > 2.5cm. Minimum duration of treatment is 4-6 weeks and response is guided by neuro imaging.
Brain abscess - HIV infected			
Toxoplasma gondii	PO Pyrimethamine 200mg X 1 day then 75mg q24h *PLUS* PO Sulfadiazine 1g q6h if < 60 kg or 1.5g q6h if > 60 kg *PLUS* PO Folinic acid 20mg q24h X 6 weeks after resolution of signs/symptoms	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (trimethoprim component) q12h X 30 days	Folinic acid prevents pyrimethamine-induced haematologic toxicity. Treat till CD4 count >200/μL for 3 months, even after complete resolution of lesions on CT/MRI.
	Suppression treatment		
	PO Sulfadiazine 2-4g in divided 2-4 doses/day *PLUS* PO Pyrimethamine 25-50mg q24h *PLUS* PO Folinic acid 20mg q24h		

<table>
<tr><th rowspan="2">Common Organisms</th><th colspan="2">Antimicrobials</th><th rowspan="2">Notes</th></tr>
<tr><th>Preferred</th><th>Alternative</th></tr>
<tr><td colspan="4">Pathogen specific</td></tr>
<tr><td rowspan="6">Cryptococcus neoformans</td><td colspan="2">Induction phase</td><td rowspan="6">For HIV infected or transplant patients, refer ID physician.

Induction phase of 6 weeks or longer in patients with neurological complications, if CSF culture is still positive after 2 weeks of treatment or if flucytosine is not given or treatment is interrupted.

In patients at low risk of therapeutic failure (early diagnosis by history, no uncontrolled underlying disease, not immunocompromised and excellent clinical response to initial 2-week antifungal combination), consider induction therapy with combination of amphotericin B plus flucytosine for 2 weeks, followed by consolidation with PO fluconazole 800mg q24h for 8 weeks.</td></tr>
<tr><td>IV Amphotericin B 0.7-1.0 mg/kg q24h

PLUS

PO Flucytosine 25mg/kg q6h

X 4 weeks</td><td>IV Liposomal Amphotericin B 3-4mg/kg q24h
OR
IV Amphotericin B lipid complex 5mg/kg q24h

PLUS

PO Flucytosine 25mg/kg q6h

X 4 weeks</td></tr>
<tr><td colspan="2">Consolidation phase</td></tr>
<tr><td colspan="2">PO Fluconazole 400 mg q24h

X 8 weeks</td></tr>
<tr><td colspan="2">Maintenance phase</td></tr>
<tr><td colspan="2">PO Fluconazole 200mg q24h

X 6 - 12 months</td></tr>
<tr><td>Mycobacterium tuberculosis</td><td colspan="2">Refer to chapter on tuberculosis</td><td></td></tr>
</table>

Bibliography:

1. The Sanford Guide to Antimicrobial Therapy 2011; 5-8, 99
2. *Clin Infect Dis* 2010; 50: 291-322
3. *Clin Infect Dis* 2008; 47: 303-27
4. *Clin Infect Dis* 2004; 39: 1267-84

SKIN AND SOFT TISSUE INFECTIONS

Skin and soft tissue infections (SSTIs) are usually caused by bacterial entry through breaches in the skin. Its clinical severity depends on host factors such as age, diabetes mellitus and state of immunocompetence.

Cellulitis

Cellulitis is an acute diffuse infection of the epidermis, dermis and subcutaneous tissue. It is usually caused by ß-haemolytic streptococci (most commonly Group A) or *S. aureus*. *S. aureus* cellulitis is usually associated with bullae or abscesses. Lack of clinical response to antimicrobials could be due to resistant strains of organisms e.g. MRSA or infection of the deeper tissues. There is growing concern regarding the emergence of community-acquired MRSA SSTIs.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
ß-haemolytic Streptococci *S. aureus*	IV Cloxacillin 2g q6h X 5-10 days	IV Amoxicillin/ Clavulanate 1.2g q8h X 5-10 days	If streptococci is cultured consider IV benzylpenicillin 4 MU q6h. IV benzylpenicillin: 1 million units = 600mg Duration of treatment depends on clinical response.

Necrotising fasciitis

Necrotising fasciitis is an infection of the deeper tissues usually involving the extremities, the parapharyngeal space, the abdominal wall or the perineum (Fournier's gangrene). Patients are generally more ill and septic. Although supportive management of organ failure and antimicrobials play a major role, surgical debridement often extensive and repeated is essential. Tissue cultures taken at the time of debridement may help to identify the organism.

There are 3 types of necrotising fasciitis. Type 1 is polymicrobial and is usually seen in patients with peripheral vascular disease, alcoholics, diabetes, chronic kidney disease and after surgical procedures. Type 2 is caused by ß-haemolytic streptococcus. It commonly occurs in patients with no medical illnesses, predisposed by blunt trauma, varicella infection, intravenous drug abuse and surgical procedures. Type 3 infection is clostridial myonecrosis, also known as gas gangrene. It often occurs in penetrating wound or crush injury associated with local devascularisation and can rapidly progress to death.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
ß-haemolytic streptococci *S.aureus* *Bacteroides spp* *Clostridium spp* Peptostreptococci Enterobacteriaceae	IV Ampicillin/ Sulbactam 3g q6h *PLUS* IV Clindamycin 900mg q8h	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Imipenem 500mg q6h *PLUS* IV Clindamycin 900mg q8h	Continue treatment until surgical debridement is no longer needed and patient has clinically improved. If *Clostridium spp* or ß haemolytic streptococci is confirmed, deescalate to IV benzylpenicillin 2 MU q4h but continue clindamycin. If streptococcal toxic shock syndrome is suspected consider IVIg.
Aeromonas hydrophila *Vibrio vulnificus*	PO Doxycycline 100mg q12h *PLUS* IV Ceftriaxone 2g q24h X 7-10 days	IV Ciprofloxacin 400mg q8h X 7-10days	If IV Clindamycin is not available, PO Clindamycin 600mg q6h may be used. *Aeromonas spp* and *Vibrio spp* need to be considered in water related injuries. At risk are the immunocompromised, diabetes and liver cirrhosis. If *Aeromonas hydrophila* is isolated to stop doxycycline.

Deep neck space infection

Deep neck space infections include the submandibular (Ludwig's angina), parapharyngeal, retropharyngeal and peritonsillar space infection. Infections of the deep neck tissues often need surgical debridement and assessment for potential airway compromise. These infections may extend resulting in mediastinitis and/or lung empyema.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Streptococcus spp Anaerobes Peptostreptococci *Fusobacterium spp* Prevotella Bacteroides (usually not *Bacteroides fragilis*)	IV Benzylpenicillin 4 MU q6h *PLUS* IV Metronidazole 500mg q8h	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/ Sulbactam 3g q6h	Most of these infections have an odontogenic source. Gram negative rods to be considered in the immunocompromised host. Continue treatment until surgical debridement is no longer needed and patient has clinically improved.

Surgical Site infection

Most surgical site infections have no clinical manifestation for the first 5 days after the operation. The most important intervention is to open the wound, drain the infected material and continue to dress the wound daily. Empiric antimicrobial is usually guided by the site of infection.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Abdominal/Perineum			
Mixed Gram-positive and Gram-negative	IV Ampicillin/ Sulbactam 3g q6h X 5-7 days	IV Piperacillin/ Tazobactam 4.5g q6h X 5-7 days	
Chest/Extremities			
S. aureus *Streptococcus spp*	IV Cloxacillin 2g q6h X 5-7 days	IV Amoxicillin/ Clavulanate 1.2g q8h X 5-7 days	

Bibliography:

1. The Sanford Guide to Antimicrobial Therapy 2011: 39-41
2. *Clin Infect Dis:* 2005: 41; 1373-406
3. *N Engl J Med* 2004: 350(9): 904-912

DIABETIC FOOT INFECTIONS

Foot infections are common complications of diabetic patients. Management of patients admitted in severe sepsis or septic shock secondary to diabetic foot infection includes intravenous antibiotics together with extensive wound debridement and/or amputation of the limb. Appropriate wound swabs should be taken prior to starting antibiotics (refer to chapter on microbiological investigations). Duration of therapy should be based on severity of infection, presence or absence of osteomyelitis and clinical response to therapy. Routinely prescribing antibiotics for a fixed duration is unnecessary.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Macerated ulcer with extensive necrosis/gangrene			
S. aureus ß-haemolytic streptococci Enterobacteriaceae *P. aeruginosa* Anaerobes	IV Piperacillin/ Tazobactam 4.5gm q6h *OR* IV Cefepime 2g q8-12h *PLUS* IV Metronidazole 500mg q8h	IV Imipenem 500mg q6h	If high risk for MRSA to add IV vancomycin.
Chronic ulcer previously treated with antibiotics			
S. aureus ß-haemolytic streptococci Enterobacteriaceae	IV Ampicillin/ Sulbactam 3gm q6h	IV Piperacillin/ Tazobactam 4.5gm q6h	

Bibliography:

1. *Clin Infect Dis* 2012: 54; 132-173
2. *World J Diabetes* 2011: 2(2); 24-32

MELIOIDOSIS

Melioidosis is a potentially fatal disease caused by *Burkholderia pseudomallei*. There is no reliable pathognomonic feature and can present as bacteremia with no obvious focal infection or as septic shock with multiorgan failure. Common sites of infection include the lung (50%), joints, spleen, liver and prostate.

Predisposing host factors for melioidosis include diabetes mellitus, renal failure, renal calculi, alcoholism, steroids, malignancy and HIV infection.

Antibiotic therapy consists of 2 phases, an initial treatment phase for 2 weeks followed by an eradication phase for 12 – 20 weeks to prevent relapse and recurrence. The actual eradication phase is guided by clinical response to therapy. Radiological imaging may be necessary to identify deep-seated abscesses that may need to be drained. Infected joints need surgical intervention.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Phase 1: Treatment			
Burkholderia pseudomallei	IV Meropenem 1g q8h (2g q8h for CNS infection) *OR* IV Imipenem 1g q8h X 14 days	IV Ceftazidime 2g q8h X 14 days	Carbapenem is preferred in severe sepsis as the benefits are: higher rate of bacterial killing in vitro due to enhanced cell wall penetration, better post-antibiotic effect and decreased endotoxin release.
	PLUS OPTIONAL IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q12h (in deep seated focal infections, neurological, joints, bones, prostate) X 14 days		
Phase 2: Eradication			
	Any 2 in order of preference: PO Trimethoprim/ Sulfamethoxazole 320:1600mg q12 h PO Doxycycline 100mg q12h PO Amoxicillin/ Clavulanate 500/125 mg q8h X 12-20 weeks		

Bibliography:

1. *Pharmaceuticals* 2010: 3; 1296-1303
2. *Med J Malaysia* 2009: 64(4); 266-274

TUBERCULOSIS

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* which may affect pulmonary and/or extra-pulmonary sites. Patients at risk of TB infections include:

- the immunocompromised (e.g. HIV, substance abuse, diabetes mellitus, malnourished, steroids, renal failure)
- close contact with a person with infectious TB disease
- persons who have immigrated from areas with high rates of TB
- groups with high rates of TB transmission e.g. the homeless, HIV patients and injecting drug users
- persons who work or reside with people who are at high risk of TB in facilities or institution e.g. hospitals, prisons.

The aim of treatment is to cure and render patients non-infectious, prevent relapse and the emergence of resistant tubercle bacilli.

The current drug regime involves the five main drugs: isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol. The treatment regime for pulmonary TB involves an intensive phase of 8 weeks and a continuation phase of 4 months.

Treatment phase	Preferred agent	Notes
Intensive	EHRZ or SHRZ q24h X 8 weeks or 56 daily doses	SHRZ is the combination of choice for **TB meningitis**. Renal profile, full blood count and liver function test should be monitored at least twice a week while the patient is in ICU. PO pyridoxine 10mg q24h should be given to prevent isoniazid induced neuropathy. Duration may be extended in the immunocompromised and in those with extrapulmonary TB. It is necessary to consult the TB specialist in the following situations:- 1. Relapse, treatment failure or treatment after interruption 2. Liver failure 3. Inability to tolerate oral medications
Continuation	HR biweekly X 4 months or 32 doses	

Drug	Dose	Max. dose	Adverse reaction
Tab Isoniazid (H)	5-8mg/kg/day	300mg	hepatitis, peripheral neuritis, hypersensitivity
Tab Rifampicin (R)	10mg/kg/day	600mg	hepatitis, vomiting, thrombocytopenia
Tab Ethambutol (E)	15-25mg/kg/day	1.2 g	optic neuritis, GI disturbances
Tab Pyrazinamide (Z)	20-40mg/kg/day	2 g	hepatotoxicity, hyperuricemia
IM Streptomycin (S)	15-20mg/kg/day	1 g	nephrotoxicity, ototoxcity, skin rash. For patients > 65 years old, dose should not exceed 750 mg
Cap AKuriT-4: Rifampicin 150mg Isoniazid 75mg Ethambutol 275mg Pyrazinamide 400mg	Body weight: 30-37kg: 2 caps 38-54kg: 3 caps 55-70kg: 4 caps > 70kg: 5 caps		

Steroids should be given in TB meningitis in non HIV patients, however the evidence is not conclusive in patients with HIV. Steroids are also indicated in TB pericarditis, TB adrenalitis and TB lymphadenitis with compressive symptoms.

Conditions	**Steroid Dose**
TB meningitis	IV Dexamethasone 0.4mg/kg/day taper over 6-8 weeks
TB pericarditis	PO Prednisolone 60mg q24h, taper over 6-12 weeks
TB adrenalitis	IV Hydrocortisone 100mg q8h and taper
TB lymphadenitis with compressive symptoms	PO Prednisolone 30-60mg q24h X 4-6 weeks

Bibliography:

1. WHO. Treatment of tuberculosis: Guidelines. 4th edition 2009
2. Guidelines on management of TB: KKM. Academy of Medicine Malaysia
3. *Clin Infect Dis* 2000; 31: 633-9

LEPTOSPIROSIS

Leptospirosis is a zoonotic infection caused by pathogenic spirochetes of the genus *Leptospira*. The clinical manifestations of leptospirosis are variable and non-specific, ranging from mild febrile illness to the icteric-haemorrhagic form with severe kidney and liver involvement and pulmonary haemorrhage.

Presumptive diagnosis is made with a positive rapid screening test such as IgM ELISA. Diagnosis is confirmed with a fourfold or greater rise in antibody titres or seroconversion in the microscopic agglutination test (MAT) on paired samples obtained 2 weeks apart. Blood for PCR testing can be done.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Leptospira spp	IV Benzylpenicillin 2 million units q6h X 7 days	IV Ceftriaxone 2g q24h X 7 days	In less severe infection: PO Doxycyline 100mg q12h x 7 days *OR* PO Azithromycin 500mg q24h x 7 days

Bibliography:

1. The Sanford Guide to Antimicrobial Therapy 2011
2. *Clin Infect Dis* 2003; 36: 1507-14

SEVERE MALARIA

Patients diagnosed or suspected with severe malaria should be started on parenteral antimalarial therapy immediately. Severe malaria with complications such as haemolysis, acute renal failure and lactic acidosis is usually due to *Plasmodium falciparum*. Patients with severe malaria are at risk of concurrent bacterial infection.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Plasmodium falciparum	IV Artesunate 2.4mg/kg at 0 hrs and 12 hrs, then q24h *PLUS* PO Doxycyline 200mg q24h X 7 days	IV Quinine Dihydrochloride 20mg/kg in 250mls D/5% over 4 hours and then 10mg / kg q8h *PLUS* PO Doxycyline 200mg q24h X 7 days	Treat severe malaria due to other plasmodium species with IV artesunate. Blood sugars and QT intervals need to be monitored regularly while on quinine. Switch to oral Artemisinin Combination Therapy (ACT) if patient is able to tolerate orally. Oral Riamet (lumefantrine and artemether) is available in Malaysia

Bibliography:

1. WHO. Guidelines for the treatment of malaria: 2nd edition 2010

CANDIDIASIS IN THE NON-NEUTROPENIC ICU PATIENT

Candidiasis is increasingly common in ICU patients and may result in high mortality especially if treatment is delayed or inappropriate. Although *Candida albicans* is the most common organism, there is a growing proportion of non-albican species, which is associated with fluconazole resistance. Other invasive fungal infections e.g. aspergillosis is rare except in neutropenic or transplant recipients.

Colonisation with candida in the oropharynx, respiratory and urinary tract is common in ICU patients. This is not an indication for treatment. Broad-spectrum antibiotic therapy increases the incidence of colonisation. Overall the risk of invasive infection increases with the number of colonised sites.

Poor outcomes are in part associated with difficulty in establishing microbiological diagnosis at an early stage of infection. Blood culture results take time and are positive in only 50% of invasive candidiasis. Nonculture-based diagnostic tests such as serological (mannan, antimannan, betaglucan) and molecular (candida-specific PCR) techniques may be useful adjuncts to early diagnosis but are not routinely available here. Scoring systems and predictive rules that combine risk factors and degree of colonisation lack sensitivity although have high negative predictive value.

Assessing risks has become the cornerstone of empiric treatment of fungal infections in the ICU setting. Patients at risk for invasive fungal infection are:

- Immunocompromised/immunosuppressive therapy
- Neutropenia (neutrophil count < 1000/mm^3)

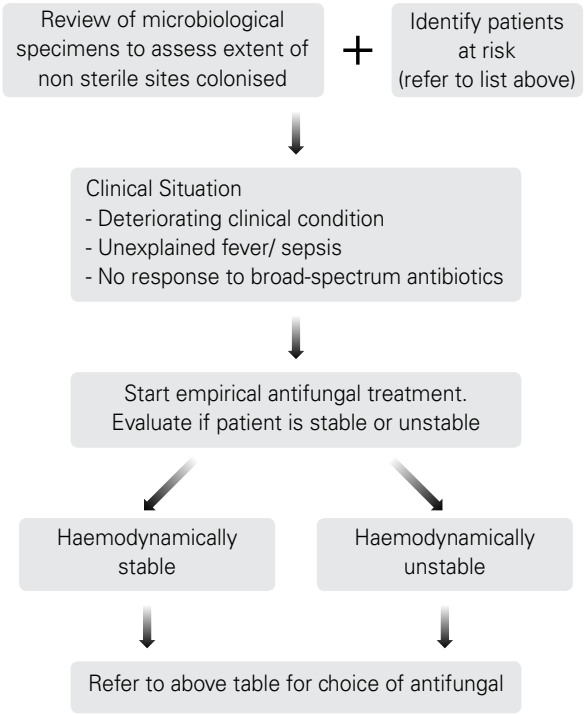
- Solid organ or bone marrow transplantation
- Candida colonisation at multiple non-sterile sites
- Use of broad-spectrum antibiotics
- Presence of central venous catheters
- Burns (> 50% BSA)
- Major trauma
- Major abdominal surgery
- Parenteral nutrition
- Severe acute pancreatitis
- High severity illness score
- Acute renal failure or haemodialysis
- Diabetes mellitus
- Prolonged ICU stay (> 7 days)

Empirical therapy should be started in a clinically deteriorating patient with unexplained sepsis who has risk factors for systemic candidiasis or has multiple site colonisation. The agent of choice depends on the causative pathogen, severity of illness and site of infection.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy in haemodynamically unstable non-neutropenic patient			
Candida spp	IV Fluconazole 800mg (loading dose) followed by 400mg q24h *OR* IV Amphotericin B 0.6-1mg/kg/day	IV Caspofungin 70mg (loading dose) followed by 50mg q24h *OR* IV Anidulafungin loading dose 200mg followed by 100mg q24h	Amphotericin B is preferred in patients with recent azole exposure (last 3 months) and at high risk of developing *C. glabrata* and *C. krusei* (e.g. severe acute pancreatitis, burns). Consider echinocandins (or lipid-based amphotericin B) in patients with recent azole exposure and renal dysfunction.
Empirical therapy in haemodynamically stable non-neutropenic patient			
Candida spp	IV Fluconazole 800mg (loading dose) followed by 400mg q24h	IV Amphotericin B 0.6-1mg/kg/day	Consider amphotericin B if patient had recent azole exposure in the last 3 months.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
C. albicans	IV Fluconazole 800mg (loading dose) followed by 400mg q24h	IV Amphotericin B 0.6-1mg/kg/day	Duration of treatment without metastatic complication is 14 days after last positive blood culture and resolution of signs and symptoms of infection. Repeat cultures every 72 hours till negative. Ophthalmic examination is recommended for all patients with candidaemia.
C. glabrata	IV Amphotericin B 0.6-1mg/kg/day	IV Caspofungin loading dose 70mg followed by 50mg q24h *OR* IV Anidulafungin loading dose 200mg followed by 100mg q24h	
C. krusei	IV Amphotericin B 0.6-1mg/kg/day	IV Voriconazole 6mg/kg q12h for 1 day followed by 4mg/kg q12h *OR* IV Caspofungin loading dose 70mg followed by 50mg q24h *OR* IV Anidulafungin loading dose 200mg followed by 100mg q24h	
C. parapsilosis *C. tropicalis* *C. lusitaniae*	IV Fluconazole 800mg loading dose followed by 400mg q24h	IV Amphotericin B 0.6-1mg/kg/day	*C. lusitaniae* may be resistant to amphotericin B.

Algorithm for empirical antifungal therapy in the non-neutropenic ICU patient



Bibliography:

1. *Ann Intensive Care* 2011; 1: 37
2. *Clin Infect Dis* 2009; 48: 503-535

APPENDIX A
DOSAGE ADJUSTMENT FOR RENAL IMPAIRMENT

Below is the formula used to calculate the creatinine clearance:

Males: Cr Cl (mls/min) = $\frac{(140 - \text{Age}) \times \text{IBW}}{0.8 \times \text{Sr. creat } (\mu\text{mol/L})}$ Females: Cr Cl (mls/min) = $\frac{(140 - \text{Age}) \times \text{IBW}}{\text{Sr. creat } (\mu\text{mol/L})}$

Drug	*Normal dose*	*Cr clearance 10-50ml/min*	*Cr clearance < 10ml/min*	*Renal replacement therapy*
Acyclovir	10mg/kg q8h	10mg/kg q12 - 24h	5mg/kg q24h	HD: 5mg/kg q24h CRRT: 10mg/kg q24h
Amikacin	Refer to Appendix B			
Amphotericin B	0.6 - 1 mg/kg q24h	0.6 - 1 mg/kg q24h	0.6 - 1 mg/kg q48h	0.6 - 1 mg/kg q24h
Ampicillin/sulbactam	3g q6h	3g q8-12h	3g q24h	HD: 3g q24h CRRT: 3g q12h
Amoxicillin/clavulanate	1.2g q8h	1.2g q12h	1.2g q24h	1.2g q24h
Benzylpenicillin	2 - 4 MU q6h	1.5 - 3 MU q6h	1 - 2 MU q6h	HD: 1 - 2 MU q6h CRRT: 2 MU q6h
Cefepime	2g q8-12h	1-2g q12-24h	0.5-1g q24h	HD: 1g q24h+extra 1g AD CRRT: 2g q24h
Cefotaxime	2g q8h	2g q12-24h	2g q24h	HD: 2g q24h+extra 1g AD CRRT: 2g q24h
Ceftazidime	2g q8h	2g q12-24h	2g q24h	HD: 2g q24h+extra 1gAD CRRT: 2g q12h
Ceftriaxone	2g q24h	Unchanged	Unchanged	Unchanged
Cefuroxime	1.5g q8h	1.5g q8-12h	1.5g q24h	HD: 1.5g q24h CRRT: 1.5g q8 - 12h

Ciprofloxacin[a]	400mg q8-12h	200mg q12h	200mg q12h	200mg q12h
Cloxacillin	2g q4-6h	Unchanged	Unchanged	Unchanged
Doripenem	500mg q8h	250mg q8 - 12h	No data	No data
Ethambutol	15-25mg/kg/q24h	15-25mg/kg/q24-36h	15-25mg/kg/q48h	HD: 15-25mg/kg after HD (3x/ week) CRRT: 15 - 25mg/kg/q24-36h
Fluconazole	400mg q24h	200mg q24h	200mg q24h	HD: 200mg after HD CRRT: 400mg q24h
Gentamicin	Refer to Appendix C			
Imipenem	500mg q6h	500mg q8-12h	250mg q12h	HD: 250mg q12h CRRT: 500mg q8h
Meropenem	1g q8h	0.5-1g q12h	0.5g q24h	HD: 0.5g q24h CRRT: 1g q12h
Metronidazole	500mg q8h	500mg q8h	500mg q12h	HD: 500mg q12h CRRT: 500mg q8h
Piperacillin/tazobactam	4.5g q6h	4.5g q8h - 2.25g q6h	2.25g q8h	2.25g q6h
Streptomycin	15-20mg/kg/q24h	15-20mg/kg/q24-72h	15-20mg/kg/q72-96h	HD: 7.5-10mg/kg after HD CRRT: 15-20mg/kg/q24-72h
Trimethoprim/ Sulfamethoxazole	5mg/kg q8h	5mg/kg q12h	5mg/kg q24h	HD: 5mg/kg q24h CRRT: 5mg/kg q12h
Vancomycin	Refer to Appendix B			

CRRT: continuous renal replacement therapy. Drug dosage adjustment during CRRT has many variables including mode of CRRT. The values here are simplified for continuous veno-venous haemofiltration (CVVH).
HD: haemodialysis AD: after dialysis
[a] Ciprofloxacin 400mg q8h to be used for *P. aeruginosa* infections

Polymyxin E

Body weight (kg)	Estimated creatinine clearance (ml/min)				
	>50	20 - 50	<20	Continuous renal replacement therapy	Intermittent haemodialysis
> 60	3 MU q8h	3 MU q12h	3 MU q24h	2 MU q12h	3 MU q24h + 2 MU AD
50 - 60	2 MU q8h	2 MU q12h	2 MU q24h	1.5 MU q12h	2 MU q24h + 1.5 MU AD
40 - 49	1.5 MU q8h	1.5 MU q12h	1.5 MU q24h	1 MU q12h	1.5 MU q24h + 1 MU AD
30 - 39	1 MU q8h	1 MU q12h	1 MU q24h	0.5 MU q12h	1 MU q24h + 0.5 MU AD

MU: million units

Sulbactam (to give in divided doses)
In Sulperazone, the ratio of cefoperazone to sulbactam is 1:1
In Unasyn, the ratio of ampicillin to sulbactam is 1:0.5

Estimated creatinine clearance (ml/min)				
>50	20-50	<20	Continuous renal replacement therapy	Intermittent haemodialysis
8g/day	6g/day	4g/day	4g/day	4g/day

APPENDIX B
THERAPEUTIC DRUG DOSING AND MONITORING

Aminoglycoside (traditional dosing/ multiple daily dosing)

Initial dose and dosing interval

Dose and interval		
CrCL (ml/min)	**Gentamicin**	**Amikacin**
> 60	1.5 - 2 mg/kg q8h	5 - 7.5 mg/kg q8h
40 - 60	1.5 - 2 mg/kg q12h	5 - 7.5 mg/kg q12h
20 - 40	1.5 - 2 mg/kg q24h	5 - 7.5 mg/kg q24h
< 20	1.5 - 2 mg/kg q48 - 72h	5 - 7.5 mg/kg q48 - 72h

In endocarditis, the dose of gentamicin is 1 mg/kg q8h when given with penicillin or cloxacillin.
(Use actual BW if malnourished and adjusted BW if > 20% ideal BW. In others, use ideal BW)

Initial assay: Trough and peak with 3rd dose

Repeat assay: Every 3 - 7 days or more frequent if changing renal profile

Sampling time: Trough: ½ hour before next dose
Peak: 1 hour at end of infusion

Target serum concentration (μg/ml):

	Peak level	
Conditions	**Gentamicin**	**Amikacin**
Pneumonia	8 - 10	28 - 35
Sepsis	7 - 10	25 - 35
Intra-abdominal	6 - 8	22 - 24
Endocarditis/UTI	4	15 - 20
	Trough level	
	Gentamicin	**Amikacin**
All conditions as above	< 2	< 8

Dose adjustment: Consult pharmacist

Aminoglycoside (high dose extended interval dosing/ single daily dosing)

Exclusion criteria:
- Age < 13
- Burns > 20%
- Ascites
- Synergistic dosing for Gram-positive infections (e.g. endocarditis)
- History of ototoxicity
- Pregnancy

Initial dose:
Gentamicin: 7 mg/kg
Amikacin: 15 mg/kg

(Use actual BW if malnourished and adjusted BW if > 20% ideal BW. In others, use ideal BW)

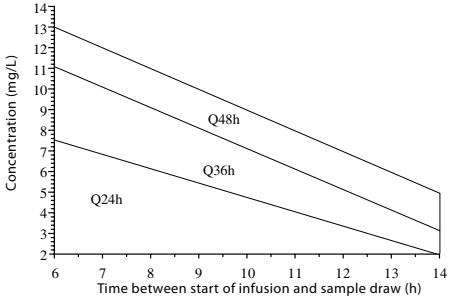
Initial assay:
Single assay 6 - 14 hours after infusion of first dose. Peak and trough serum levels are not routinely done.

Repeat assay:
Once weekly or more frequent in patients requiring q36h or q48h dosing, changing renal function or on other nephrotoxic drugs.

Dosing interval following 1st dose:
For gentamicin, plot concentration on the Hartford nomogram below to determine the dosing interval.
If the level:
- falls on a borderline, use the longer interval.
- falls above the q48h dosing interval, reevaluate the need for continued therapy
- is < 2 µg/ml, and continue current regimen if the patient is clinically stable or improving. If not, re-evaluate clinical situation (e.g. repeat level, change to traditional dosing, change antibiotics)

For amikacin, divide the measured concentration by 2 before plotting on the nomogram to determine the dosing interval.

Hartford Hospital High Dose Extended Interval Aminoglycoside Nomogram



Applicable only to gentamicin dosing of 7mg/kg (or amikacin 15mg/kg)
Unit: mg/L = ug/ml

Calculation of ideal and adjusted body weight in kg

Ideal weight (male): 50 + [0.9 x (height in cm - 150)]
Ideal weight (female): 45 + [0.9 X (height in cm - 150)]
Adjusted weight: 0.4 (Actual BW – Ideal BW) + Ideal BW

Vancomycin

Loading dose: (use actual BW) 25 - 30mg/kg (not to exceed 2g per dose)
Consider in seriously ill patients i.e. severe sepsis, meningitis, pneumonia, endocarditis.

Maintenanace dose: (use actual BW) 15 - 20mg/kg/dose

Dosing interval: (based on creatinine clearance)

CrCl (mL/min)	Dosing Interval
> 50	q12h
30 - 50	q24h
< 30	single dose, then check random level in 24 - 48 hours, redose when level is below therapeutic level
Haemodialysis	500 - 750mg after each haemodialysis

Initial assay:	Trough level before 4th dose if renal function remains stable.
Repeat assay:	Once-weekly monitoring in haemodynamically stable patients. More frequent or daily monitoring in patients who are haemodynamically unstable and changing renal function.
Sampling time:	Trough: 30 mins prior to next dose. Peak: not recommended due to extreme inter-patient variability and lack of correlation with either efficacy or toxicity.
Target serum concentrations (trough):	10 - 15 µg/ml in conditions other than listed below. 15 - 20 µg/ml in bacteremia, endocarditis, osteomyelitis, meningitis, pneumonia. For isolates with MIC of 1 - 2 µg/ml, the minimum trough concentration should be at least 15 - 20 µg/ml.
Dose adjustment (based on trough concentration)	If < 10 µg/ml (or < 15 µg/ml in target levels of 15 - 20 µg/ml), decrease the dosing interval by one step in steps of q12h, q24h, q36h, and q48h. If receiving the dose q12h, increase the dose by 250 - 500mg or consider q8h. If > 15 µg/ml (or > 20 µg/ml in target levels of 15 - 20 µg/ml), increase the dosing interval by one step.

Bibliography:

1. Therapeutic Guidelines: Antibiotic, Therapeutic Guidelines. Edition 14, Melbourne, Victoria 2010
2. *Am J Health Syst Pharm*: 2009; 66:82-98
3. Bedside ICU Handbook: Tan Tock Seng Hospital, Singapore. 2nd Edition 2007

APPENDIX C
EXTENDED INFUSIONS OF ß-LACTAMS

The use of extended infusions of ß-lactam antibiotics has been shown to improve the time the free drug remains above MIC that predicts the killing characteristic of the antibiotic. The ambient temperature for the antibiotic infusions should be 25ºC or less to ensure stability. A loading dose must be given prior to regular dosing of the antimicrobial.

Do not infuse the antibiotics with omeprazole, pantoprazole or magnesium sulphate infusions

Antibiotic	Loading dose over 30mins	Duration of infusion	Dilution
Meropenem	1-2g	Extended over 4 hours	500mg or 1g: dilute in 50mls normal saline. 2g: dilute in 100mls normal saline
Imipenem	500mg	Extended over 4 hours	250mg, 500mg or 1g: dilute in 50mls normal saline.
Doripenem	500mg	Extended over 4 hours	500mg: dilute in 50mls normal saline
Piperacillin/ Tazobactam	4.5g	Extended over 4 hours	2.25g or 4.5g: dilute in 50mls normal saline.
Cefepime	1-2g	Continuous infusion over interval prescribed	1 or 2 g: dilute in 50mls normal saline. For q24h, infuse at rate of 2mls/h For q12h, infuse at rate of 4mls/h For q8h, infuse at rate of 6.2mls/h
Ceftriaxone	2g	Continuous infusion over interval prescribed	1-2g: dilute in 50mls normal saline For q24h, infuse at rate of 2mls/h For q12h dose, infuse at rate of 4mls/h

Antibiotic	Loading dose over 30mins	Duration of infusion	Dilution
Ceftazidime	2g	Continuous infusion over interval prescribed	1-2g: dilute in 50mls normal saline For q24h, infuse at rate of 2mls/h For q12h, infuse at rate of 4mls/h For q8h, infuse at rate of 6.2mls/h

Reconstitution directions

1. Each vial should be reconstituted with water or 0.9% sodium chloride (as per the usual practice) and then dilute the reconstituted solution with 0.9% sodium chloride to a volume of 50mls or 100mls.

2. Infuse over 4 hours immediately to reduce the risk of microbial contamination.

3. Flush IV access before and after infusion of the antibiotic with 0.9% sodium chloride.

4. Preferably to infuse the antibiotic using a dedicated iv access.

5. The ambient temperature for the infusions of antibiotics should be 25°C.

Guide to Antimicrobial Therapy in the Adult ICU 2012

ISBN 978-967-11415-0-2

9 789671 141502